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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

Received

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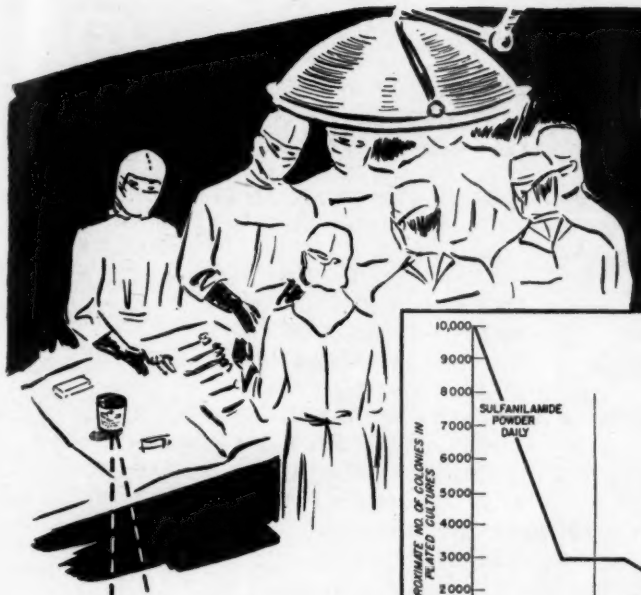

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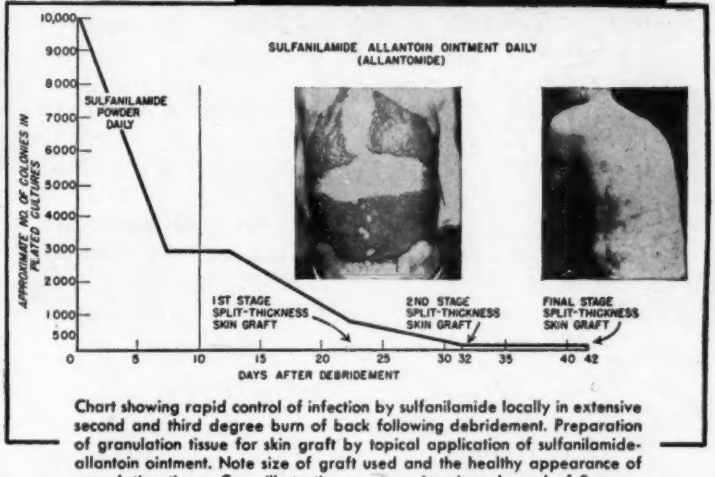

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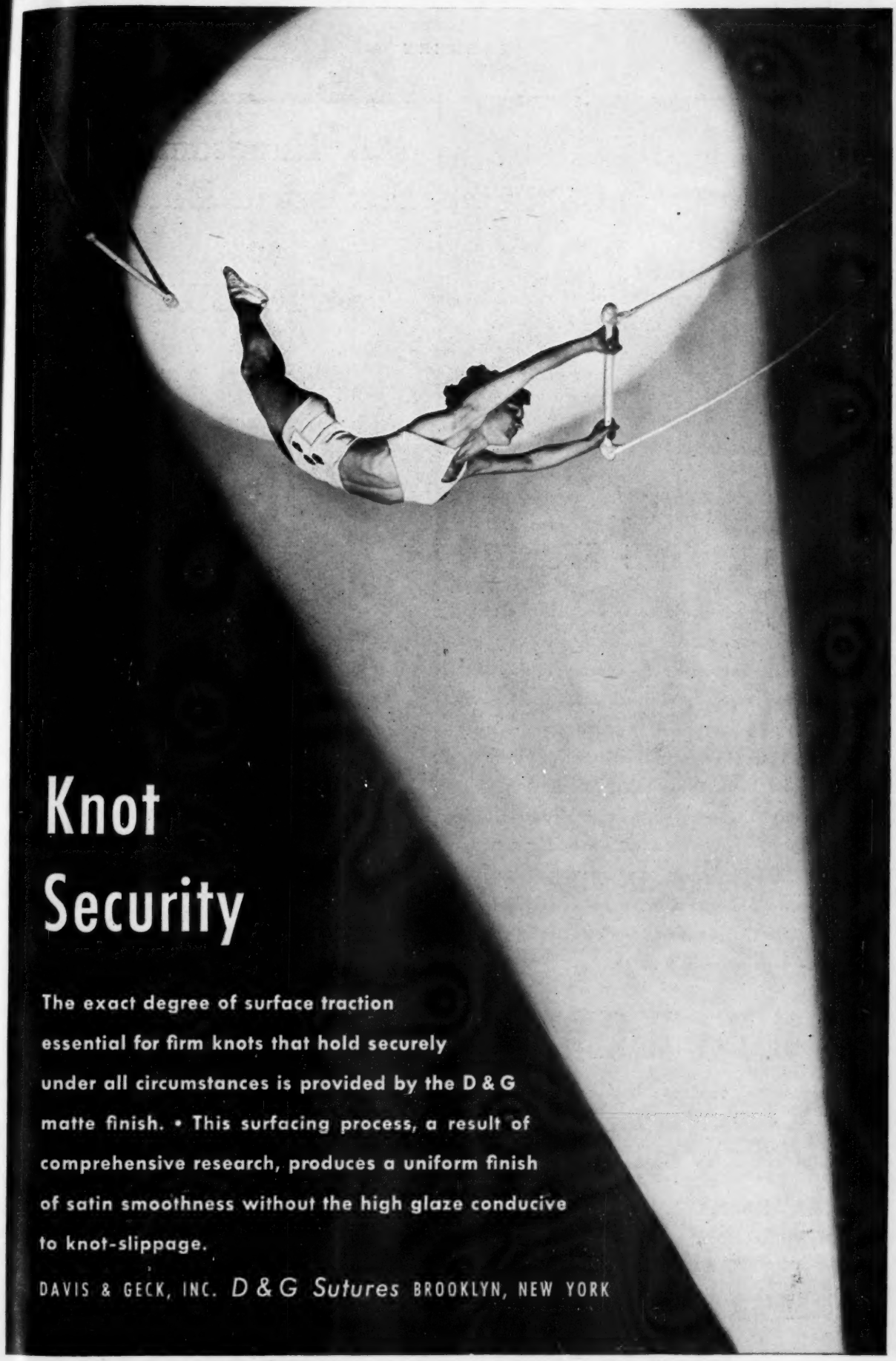

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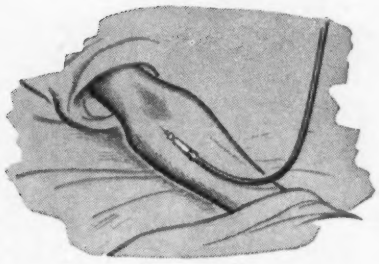

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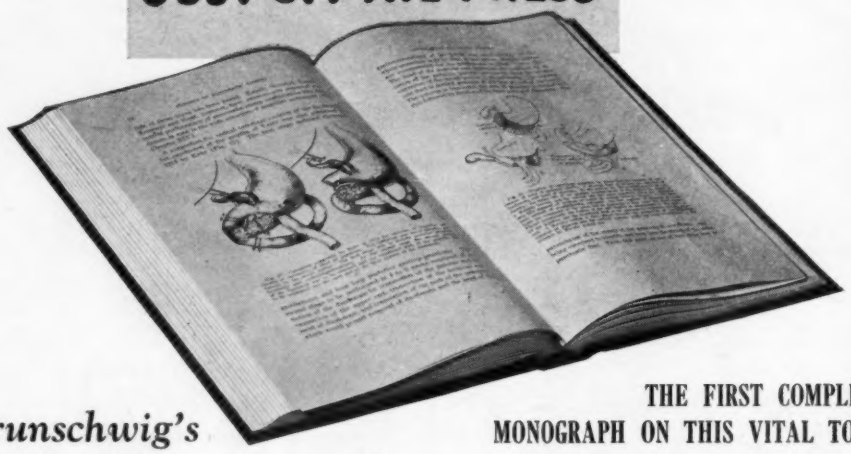

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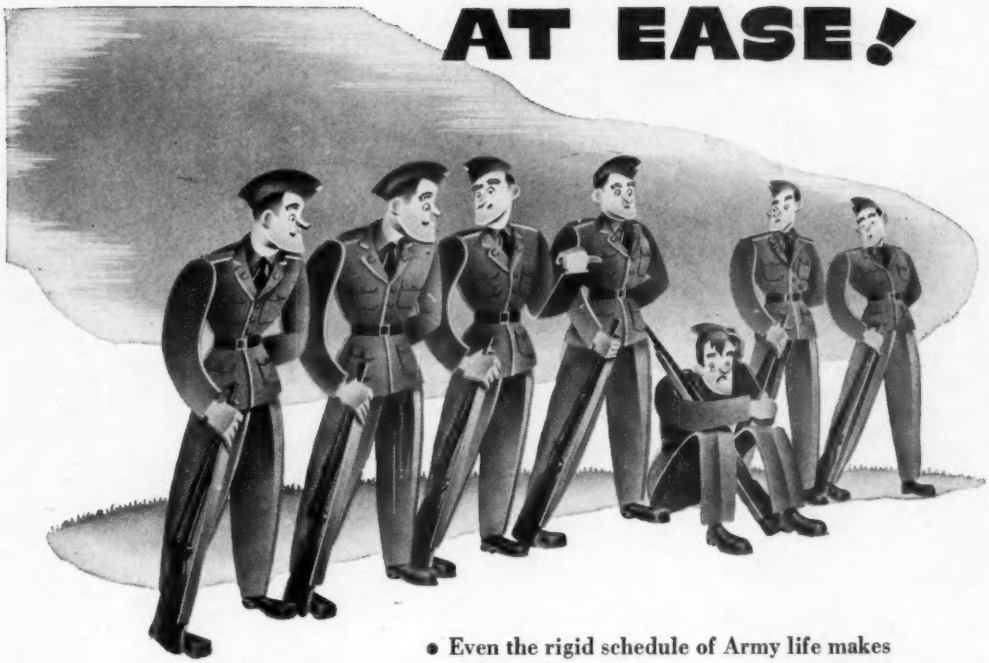

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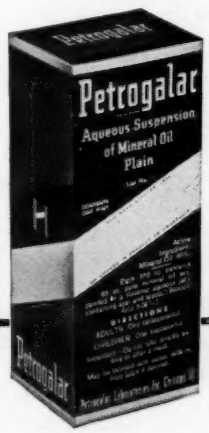

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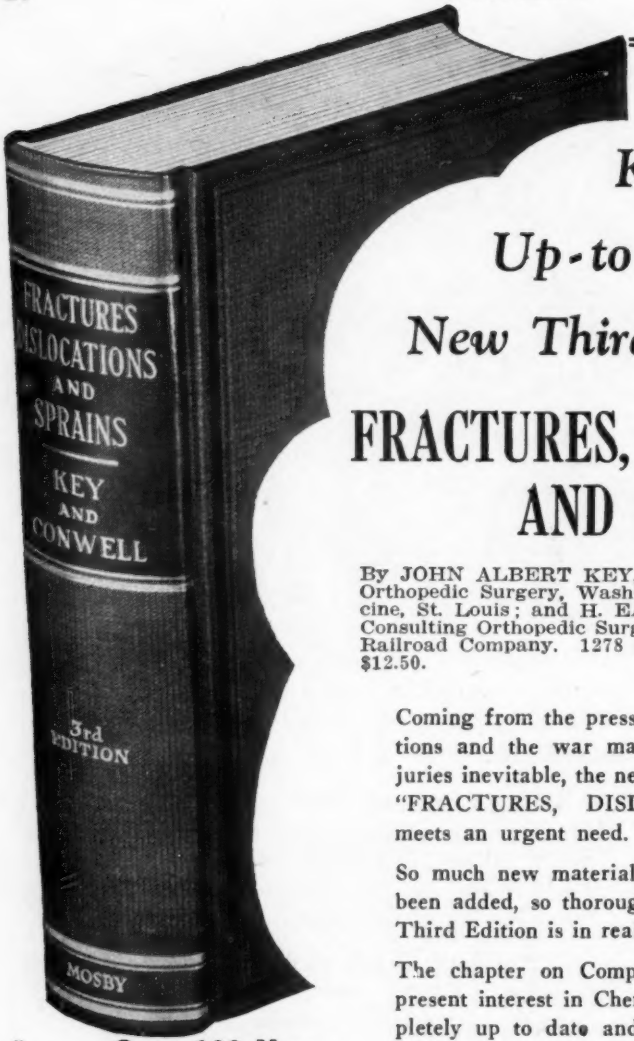

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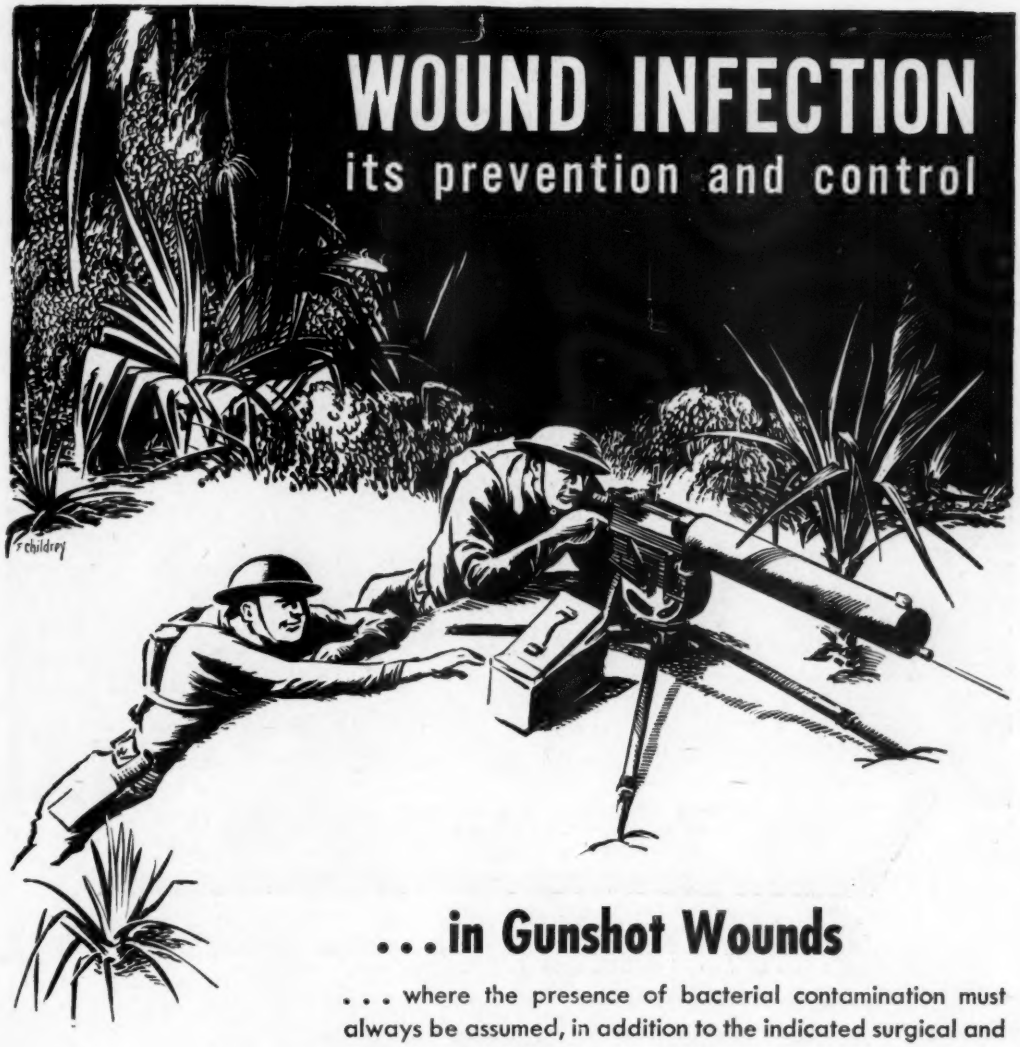

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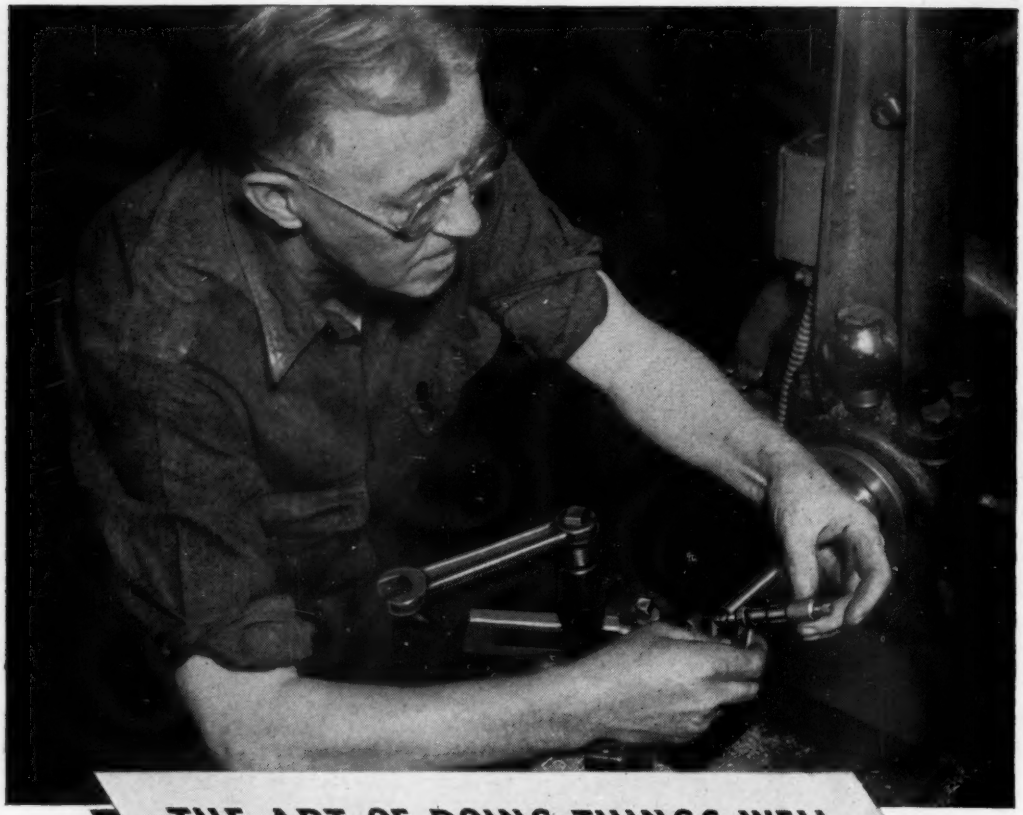

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Original Communications

THE APPLICATION OF PHLEBOGRAPHY TO THE THERAPY OF THROMBOSIS AND EMBOLISM

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INCREASING clinical interest in the problems of thrombosis and embolism has led to the frequent use of phlebograms, not only for diagnosis, but, in many cases, to furnish necessary preoperative information. While a few sporadic radiographic studies of the venous system were made in the Massachusetts General Hospital in the past, our experience has been gained almost entirely within the last year. During this period phlebograms of slightly over 100 lower extremities have been made by various members of our peripheral vascular clinic. It has been possible to check anatomically the accuracy of the radiographic interpretations in many of these cases, since, to this date, seventy-three patients have had exploration and ligation of the femoral vein performed (nine of this latter group had bilateral ligations).

Great credit must be given to dos Santos[1] and to Bauer[2] for their introduction and elaboration of the phlebographic technique, with its application to the disease of thrombo-embolism. After studying their monographs, it is easy to become extremely enthusiastic about the method. Critical evaluation has substantiated many features, but has also discovered certain limitations that must be recognized. Some of the problems that have developed have been noted by Dougherty and Homans,[3] but are important enough to merit further discussion.

METHODS

The first problem involves the production of an accurate phlebogram. This should demonstrate, so far as possible, the patency or block of all

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parts of the venous system of the extremity. We have used several different methods, varying in so far as the site and method of injection are concerned. The details of the radiograph and of the medium employed have been the same in all instances. The methods are as follows:

1. In the early cases Bauer's technique was used as a routine method. After novocain infiltration, a 2 cm. incision at right angles to the Achilles tendon, just behind the external malleolus, is made. The terminal branch of the short saphenous vein is isolated in the subcutaneous tissue. A No. 18 ball-pointed needle, inserted proximally, is tied into the vein. The patient is then placed flat on his back with the heel elevated on a four-inch block. The leg is internally rotated ten to fifteen degrees to secure the widest gap between the tibia and fibula when the picture is taken. Two large x-ray casettes are placed in tandem beneath the leg. The lower should extend a short distance above the knee, since a short blank space will appear between the two casettes, and should not include this important area. The focal length of the tube must be about six feet, since the entire leg must be included in the field. Twenty-five cubic centimeters of diodrast are then injected at a steady rate, so that exactly sixty seconds are consumed. At this time, just at the conclusion of the injection, using soft-tissue technique, the x-ray exposure is taken. A normal phlebogram obtained in this manner is shown in Fig. 1.

The advantages of Bauer's technique are that the same vein is used in all instances so that all phlebograms are comparable in that respect. Occasionally it is difficult to isolate the terminal branch of the short saphenous vein and requires a minor operative procedure. A more important criticism is that the deep venous system may not be delineated accurately. An interesting case brought this to our attention.

E. W. (M. G. H. No. 208227), a 62-year-old female, entered the hospital because of varicose veins. She gave a history of phlebitis on the right (twenty-five years previously), followed by mild chronic swelling, but no ulceration. In order to determine the status of her deep venous system, a phlebogram (Fig. 2A) was done by the method of Bauer. Apparently there was complete block of the deep veins, the diodrast returning entirely by the long saphenous vein. Clinical tests, however, indicated that the femoral vein was not occluded and the long saphenous vein was incompetent. Accordingly, the saphenous vein was ligated at the sapheno-femoral junction. A day thereafter, a repeat phlebogram (Fig. 2B) showed that the deep venous system was patent. Irregular filling of the femoral vein indicated that the vein had been recanalized after the previous attack of phlebitis.

Thus, absence of filling of a deep vein may be due to the preferential return of dye by another route. The patients who have a long history of deep phlebitis and have developed long saphenous varicosities often present a confusing picture. Phlebograms will usually show no filling of the femoral vein with the long saphenous or other collateral veins clearly outlined. Bauer believed that this meant the

femoral vein had been obliterated by the phlebitic process. However, clinical tests have made us certain, in nearly all cases we have observed, that the femoral vein is patent. Absolute permanent obliteration of the femoral vein must be extremely rare.

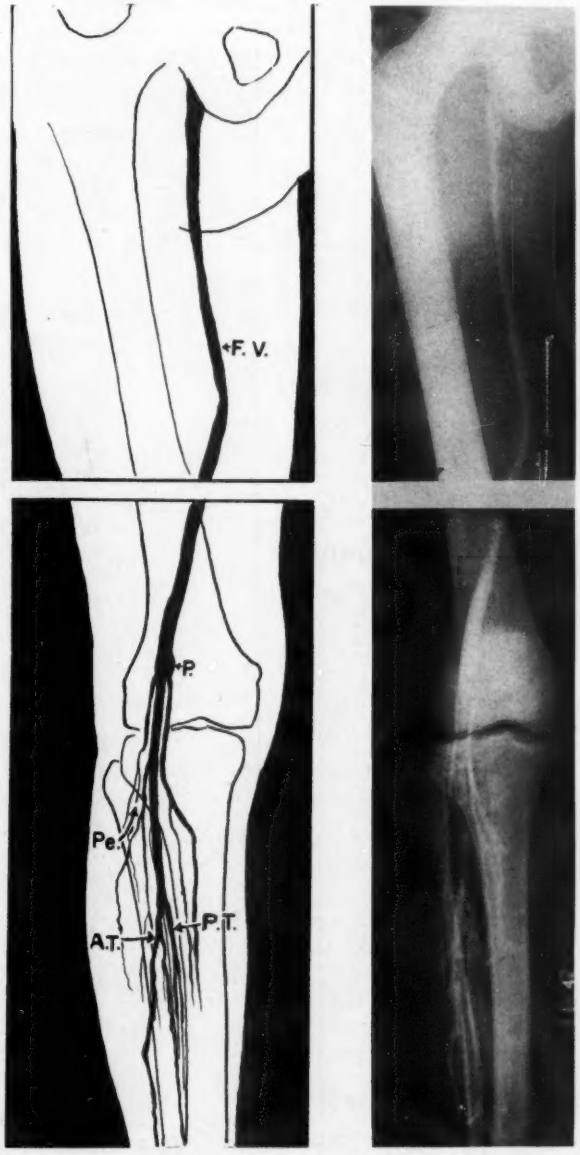

Fig. 1.—P. W., normal phlebogram. Note the femoral vein (*F.V.*) in which valves can frequently be seen, the popliteal vein (*P.*), and numerous branches in the lower leg, of which the most important are the anterior tibial (*A.T.*), posterior tibial (*P.T.*), and peroneal (*Pe*).

It appears, therefore, that preferential return of the diodrast by way of the long saphenous vein, if the patient has had previous deep phlebitis, may lead to an erroneous impression concerning the patency of the femoral vein. To obviate that objection, the next method was employed.

2. The technique is the same as that of Bauer, except that a blood pressure cuff with a pressure of 20 mm. of mercury is applied to the lower leg, the upper level being at the mid-calf. Accordingly, the long saphenous vein is occluded by the tourniquet so that all of the injected diodrast must flow through the deep femoral system.

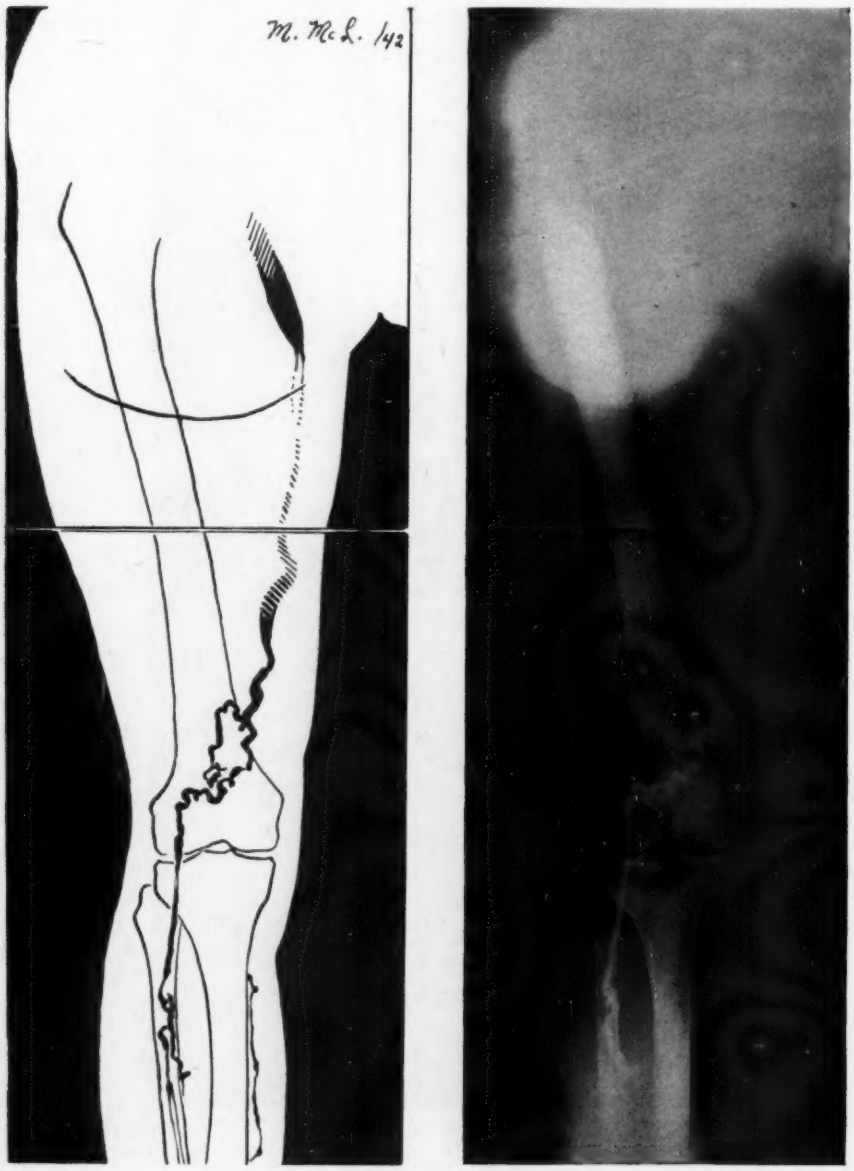

Fig. 2A.—E. W. (M. G. H. No. 208227), preoperative phlebogram. Deep phlebitis twenty-five years previously, incompetent long saphenous vein. Note the absence of filling of the deep venous system. Diodrast outlines only superficial veins and the long saphenous vein in the thigh.

Use of this method means that the presence or absence of thrombosis in the long saphenous vein cannot be determined accurately from the

phlebogram. This can, however, be almost surely detected clinically because of the superficial location of the vein. It is important also to note that a pressure of as much as 40 mm. of mercury may be necessary to occlude some sclerosed, varicose saphenous veins completely, but that too great a tension in the cuff may compress the deep as well as the superficial system.

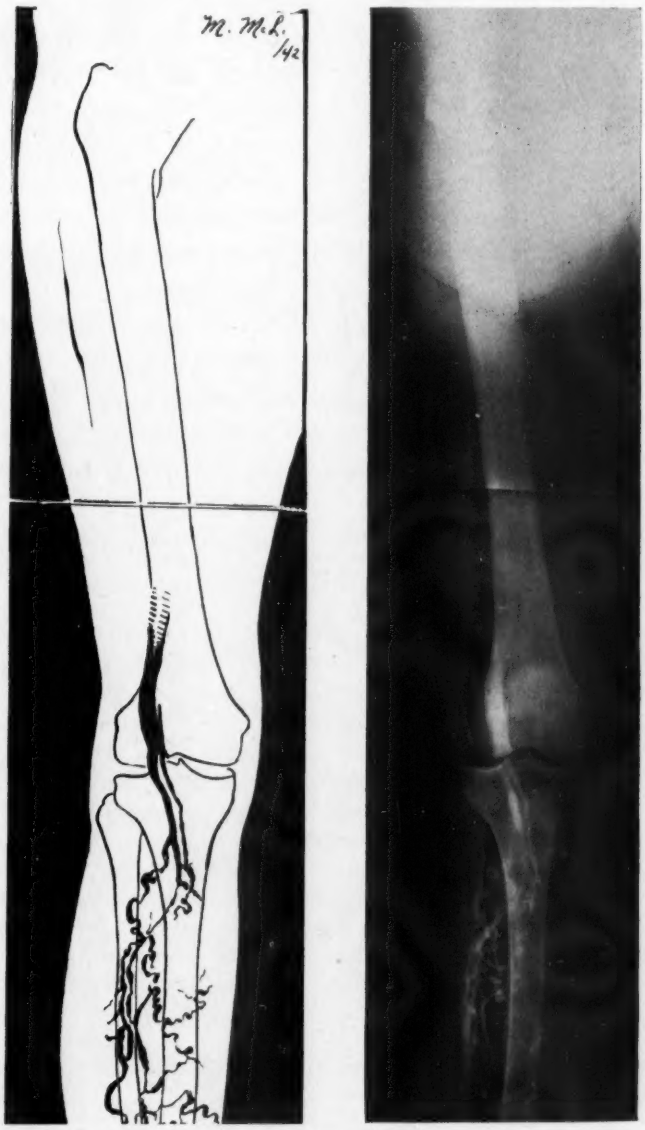

Fig. 2B.—E. W. (M. G. H. No. 208227), postoperative phlebogram. After high saphenous ligation, the phlebogram demonstrates a patent popliteal and lower femoral vein.

3. The injection is made into one of the dorsal veins of the foot, or the distal end of the long saphenous vein. Return of blood through the

long saphenous vein is prevented by the use of a tourniquet as described above. Prompt filling, primarily of the posterior tibial vein by means of numerous perforating vessels in the lower leg, is obtained.

This method, suggested by Linton,[4] is the simplest to employ, and has produced radiographs that are as accurate as those produced by the more cumbersome procedure.

All of these methods are subject to certain theoretical objections. In the first place, it seems improbable that all the main venous channels could be filled by injection of the terminal end of either the long or short saphenous vein, despite the presence of numerous communicating veins. Also, the venous pattern in the lower leg is not constant enough to make it possible to be certain that thrombosis is present when only a portion of one of the main veins has been thrombosed. Further, if the thrombosis has originated in one of the muscular veins of the calf, as the studies of Hunter, Sneeden, Robertson, and Snyder[5] have shown is the most common source, or in the plantar veins, the phlebogram will not become positive until the major venous channels are involved.

It follows that in certain instances thrombosis of certain veins of the lower leg may exist despite an apparently normal phlebogram. The clinical diagnosis of thrombosis was made in three of our patients at a time when the phlebogram showed normal filling of the main veins. At a later date, the occurrence of emboli led to a repetition of the phlebogram, which was positive in the three cases.

J. B. (M. G. H. No. 276939) was a 45-year-old man who had a laminectomy for the removal of a ruptured intervertebral disc on April 16, 1941. Ten days after operation he had the sudden onset of tenderness in the left calf and over the course of his femoral vein to the groin, and a positive Homans' sign. No edema was present. A phlebogram done two hours after onset (Fig. 3A) showed no definite abnormality. In view of this finding the patient was heparinized and within twenty-four hours his leg symptoms had entirely disappeared. Seven days later, after a continued irregular temperature record, he had signs of pulmonary infarcts, later confirmed by x-ray. Re-evaluation of the legs proved them to be again entirely negative clinically. However, bilateral phlebograms were done which proved the right to be normal, but the left leg now showed the femoral system to be occluded (Fig. 3B). Femoral exploration confirmed the femoral thrombosis. Some free thrombus was removed and the vein ligated. The patient recovered with no further difficulty.

It seems, therefore, that the phlebogram cannot be considered absolutely reliable in so far as the diagnosis of thrombosis is concerned. Certainly there are many cases in which a leg appears clinically normal, while the phlebogram will show the presence of a deep thrombosis. On the other hand, if clinical signs indicate that thrombosis is present, and if the phlebogram is indeterminate or negative, the patient should be considered to have thrombosis, and therapy should be determined on that basis.

INDICATIONS

In general phlebograms are valuable (1) in any case of known or suspected thrombosis of the veins of the lower leg, or (2) after a pulmonary infarct has occurred, unless it unquestionably has arisen from

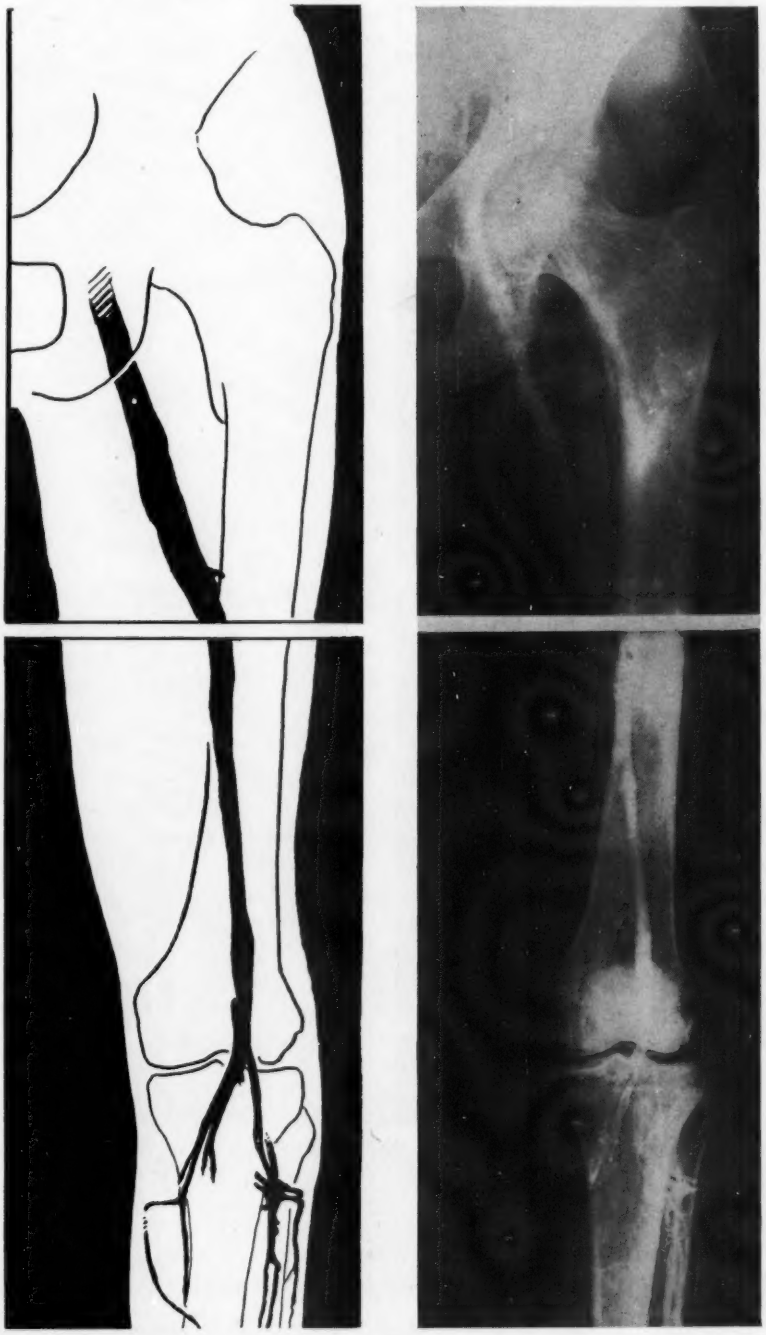

Fig. 3A.—J. B. (M. G. H. No. 276939). Phlebogram taken two hours after onset of deep phlebitis revealed no definite evidence of thrombosis.

elsewhere than the leg. Because thrombosis is so frequently bilateral, many patients will require bilateral procedures. The two phlebograms

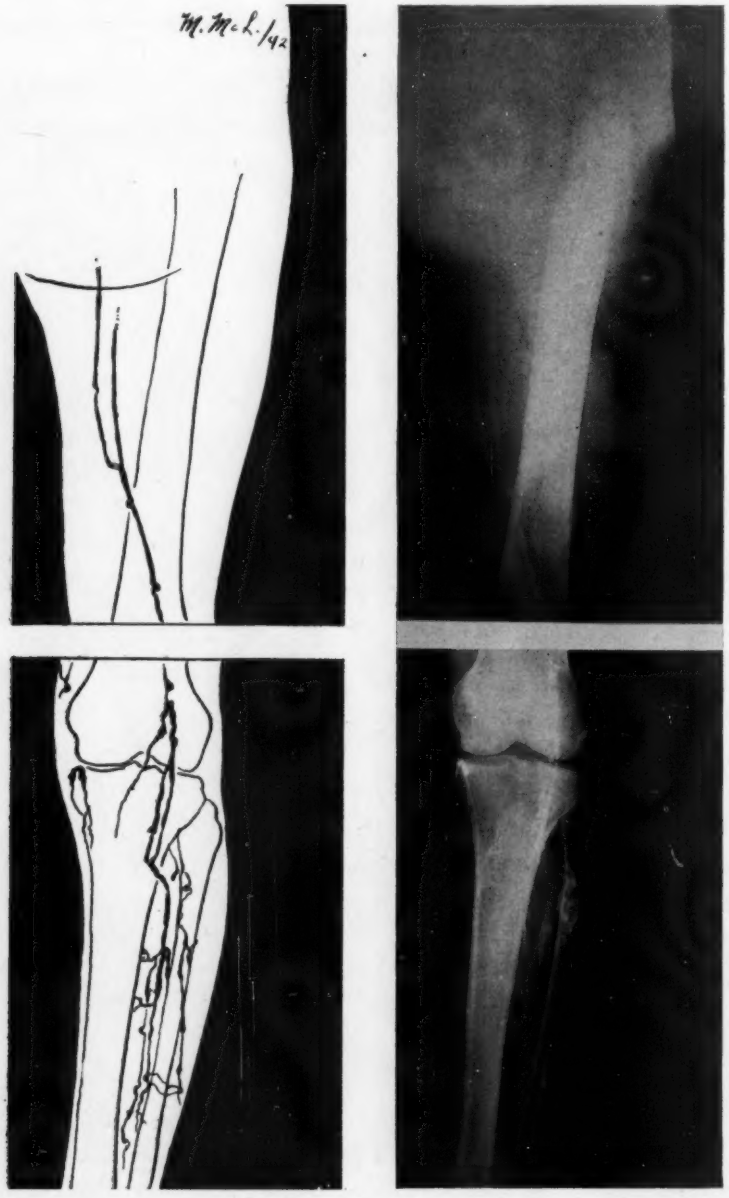

Fig. 3B.—J. B. (M. G. H. No. 276939). Phlebogram done two weeks after that shown in Fig. 3A. Observe obliteration of the femoral vein with return of diodrast by collateral vessels.

may be taken one after the other without risk. The existence of a superficial thrombophlebitis constitutes a special indication for a phlebogram, since involvement of the deep system will be found to occur quite commonly in conjunction with thrombosis of the saphenous vein.

We have expected that certain systemic manifestations might occur after the injection of the 50 c.c. of diodrast that are required for the production of bilateral phlebograms. Up to the present time, none has occurred. It has been suggested that the chemical irritation of a vein by the diodrast may be sufficient to initiate venous thrombosis. Another objection raised is that thrombi might be mechanically dislodged by the introduction of the diodrast. It is possible that both of these objections are valid in rare instances; we have not, however, seen any evidence to support them, and are convinced that the practical results completely overweigh these theoretical considerations.

One contraindication to a phlebogram is the presence of sepsis about the ankle. Usually some vein in normal tissue can be utilized, but occasionally none is available.

APPLICATION

The phlebogram, to be considered of any important value, must furnish information that is not demonstrable by astute clinical examination. Of course it does provide, in addition, a permanent record of the extent of the thrombosis that is of importance in the study of any series of cases.

The inaccuracy of clinical examination in any case of thrombosis is notorious, and has been discussed so frequently that it is unnecessary to do so again. It has already been pointed out by Fine and Sears[6] that many previous studies of thrombo-embolic problems have been entirely misleading since the venous systems involved have not been noted accurately.

Certain groups of cases demonstrate the value of the phlebogram most clearly. They will be illustrated by case reports:

1. The diagnosis of thrombosis is important, even though no specific therapy is contemplated. Occasionally a patient in his postoperative course will develop fever and elevated pulse. Other possible complications may be ruled out, and the diagnosis of thrombophlebitis made by a phlebogram.

F. G. (M. G. H. No. 305431) was a 22-year-old female who was admitted to the hospital for an elective cholecystectomy. Two weeks after operation, just after the common duct tube was removed, she began to run a temperature of 102° F. It was believed that she was developing a subdiaphragmatic abscess. Two days later slight tenderness in the left groin, and a one-inch increase in circumference of the thigh suggested the possibility of deep phlebitis. The diagnosis was established by means of a phlebogram (Fig. 4) which showed a block of the femoral vein. No further investigations of the subdiaphragmatic area were made and the patient was treated conservatively for the phlebitis, because of her youth. She recovered without incident and left the hospital two weeks later.

2. Pulmonary infarcts have occurred, with no evidence of the source. Phlebograms of the legs may show the source of the emboli, and ligation of the femoral vein will result in cure.

T. K. (M. G. H. No. 235921) was a 55-year-old man with long-standing rheumatic heart disease and fibrillation, who was admitted to the medical service with a diagnosis of bronchopneumonia. He had had "grippe" one week previously and had

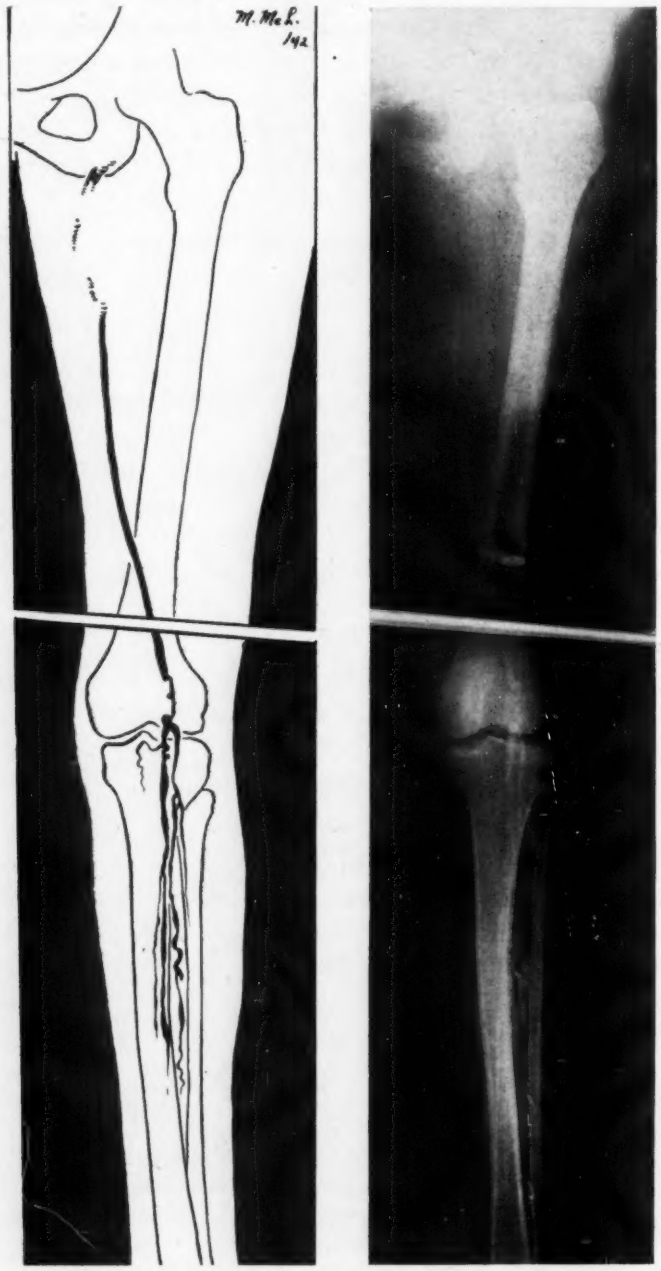

Fig. 4.—F. G. (M. G. H. No. 305431). Note the obliteration of the femoral system.

raised blood-streaked sputum for three days prior to admission. The x-ray showed a poorly defined area of density thought to be consistent with lobar pneumonia. During the next four weeks his course was irregular but at no time was a positive

culture for pneumococcus obtained. Two weeks after admission an x-ray showed an area of consolidation in the right lower lobe, and five days later, a process lateral to the hilum on the left, which was interpreted as a pulmonary infarct. Shortly thereafter, his status improved and he was allowed out of bed. He then, for the first time, complained of a little pain over the left calf and measurements showed three-fourths of an inch swelling on the left, with negative Homans' sign. Since no previous observations had been made of the circumference of his legs, it was uncertain whether or not this finding was of consequence. On the other hand, his phlebograms were striking for they showed filling along the course of a clot in the femoral vein, the head of which was just above the mid-thigh (Fig. 5). Exploration of the femoral vein was carried out at this level and a clot was found incompletely fixed to the vein wall. Following this he recovered rapidly and was discharged.

3. An acute superficial thrombophlebitis is present. A phlebogram of the involved extremity is indicated. Frequently an associated, widespread thrombosis of the deep venous system will be found.

J. L. (M. G. H. No. 289805), a 63-year-old man, had a two-stage resection of the rectum for carcinoma. Nine days following the second stage, he developed an area of swelling and redness over the course of the left long saphenous vein in the region of the knee. Homans' sign was negative and measurements of the legs were equal except below the knee at the level of the localized obvious swelling. Here the leg was one inch larger. During the next twenty-four hours the superficial phlebitis progressed to above the knee, though the swelling remained localized. We had discussed the use of phlebography prior to this case and although all the evidence pointed to a superficial process, we made our first phlebogram on this man (Fig. 6). Much to our surprise, there was occlusion of the entire deep venous system. Femoral exploration proved the presence of a large, soft thrombus which extended above the sapheno-femoral junction. This was removed and the vein ligated. Recovery was uneventful.

4. The presence of a deep thrombosis is suspected and immediate therapy is contemplated. The early detection of thrombosis is essential if treatment is to be instituted before emboli have occurred. Hence, phlebograms are performed as emergency procedures day or night on the slightest indication. Many different types of pictures are obtained. The most common are as follows:

(a) Massive thrombosis of all main deep venous channels. In the usual case, practically no veins are visible on the x-ray plate. All the diodrast that is injected fills a constricted saphenous vein, and the deep veins are not visible at all. This was the most common picture obtained early in the study when phlebograms were often delayed many hours for various considerations; it is a later stage of thrombosis. Exploration of the femoral vein will usually reveal recently formed thrombus in the common femoral and external iliac veins. The thrombus must be removed by the Trendelenburg suction device before ligation of the vein.

J. O. (M. G. H. No. 336852) was a 66-year-old man who had a spontaneous onset of throbbing pain in his right instep and sole of his foot eight days before entry.

Shortly thereafter, slight swelling developed in his foot and his podiatrist recommended new shoes. In spite of this, pain and swelling persisted and he then consulted his physician, who ordered rest and hot water bottles to the leg. Since

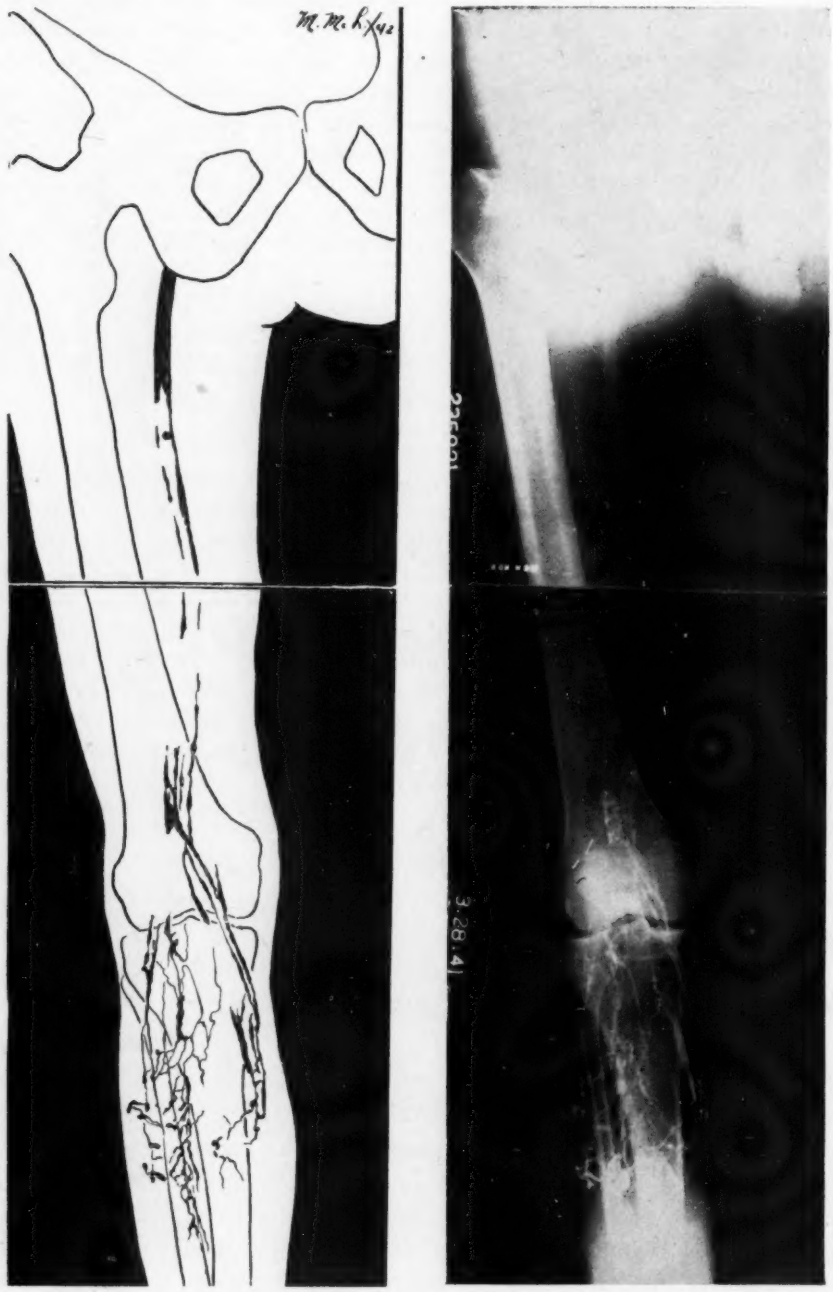

Fig. 5.—T. K. (M. G. H. No. 235921). There is complete thrombosis of the lower two-thirds of the femoral vein and partial filling in the lower leg.

there was no improvement, he was admitted to the hospital. No tenderness was elicited along the superficial or deep venous trunks. A phlebogram (Fig. 7) revealed typical deep venous occlusion which was confirmed by femoral exploration. A

large clot with a free-lying tip was extracted from the proximal end of the vein. The common femoral vein was divided and ligated. The patient recovered without complication and left the hospital ten days later.

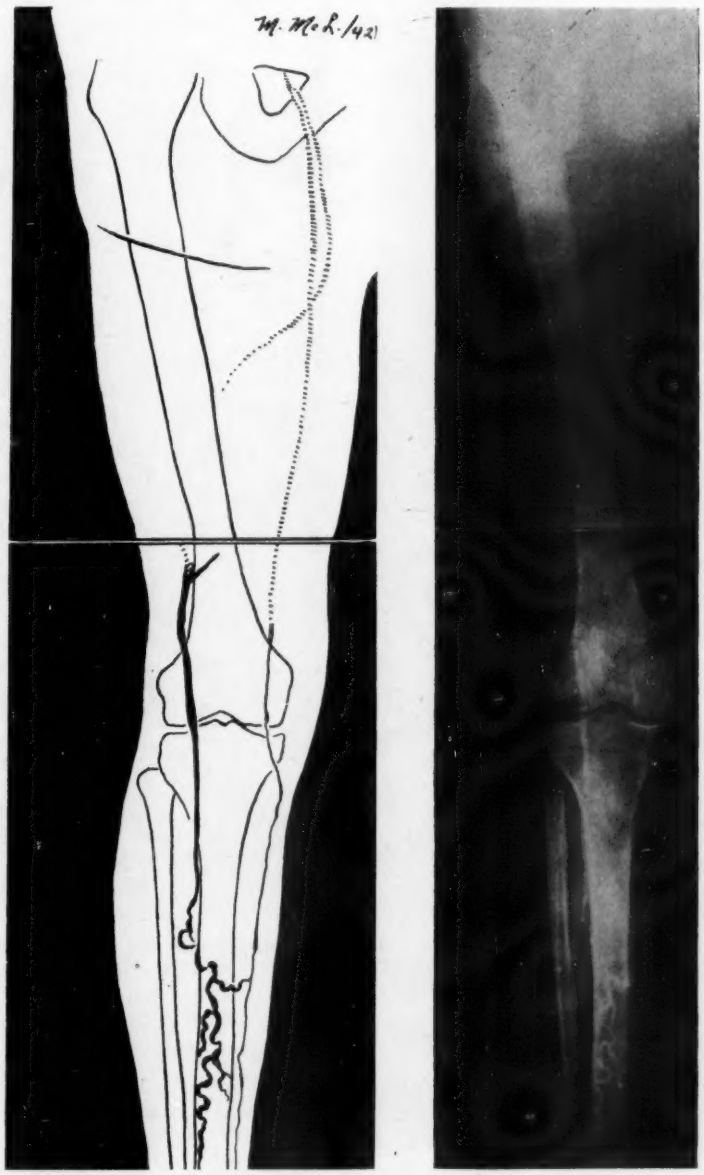

Fig. 6.—J. L. (M. G. H. No. 289805). Acute superficial and deep thrombophlebitis. Note the almost complete lack of filling of veins and the total absence of the normal pattern.

(b) Thrombosis of the veins of the calf. One or all of these vessels may be thrombosed. If all are thrombosed, interpretation is easy, but if only one vein is not filled, the radiographic interpretation is likely to vary with different observers. A phlebogram of the opposite leg is especially valuable as a control in this group of cases.

T. I. (M. G. H. No. 319658), a 47-year-old Polish woman, entered the hospital on Sept. 9, 1941 with an appendiceal abscess. On conservative management she improved steadily and became essentially afebrile by her fifteenth hospital day. She was then allowed out of bed for the next three days, but her temperature gradually rose to 100° F. During the afternoon of the third day, she complained of

Fig. 7.—J. O. (M. G. H. No. 336852). Acute deep thrombophlebitis. The long saphenous vein fills normally, but the deep system is not visualized.

sharp, transitory pain in her left chest. The chest x-ray was negative for infarct. The following morning the patient complained of pain low in the left calf. Examination revealed a well-localized area of tenderness over the Achilles tendon, but no measurable swelling. The tissues over this level felt thickened. A phlebogram (Fig. 8) showed obstruction of the posterior tibial vein. This patient refused any operative procedure and was discharged shortly.

P. B. (M. G. H. No. 329354), a 59-year-old male, had a two-stage resection of carcinoma of the hepatic flexure, complicated by a duodeno-colic fistula. Ten days after his first stage, he developed fever, slight right calf tenderness, and two-inch swelling of the right calf. The right femoral vein was explored after the phlebogram demonstrated complete deep venous occlusion and a large, soft thrombus was removed. The following day he had moderate swelling on the left side. Here the phlebogram demonstrated femoral patency, but block of the deep channels below the mid-popliteal level (Fig. 9). The left superficial femoral vein was immediately

ligated and found to be patent. The patient later survived resection of the colon and duodenum, leaving the hospital eight weeks after his vein ligation, with no other thrombo-embolic complication.

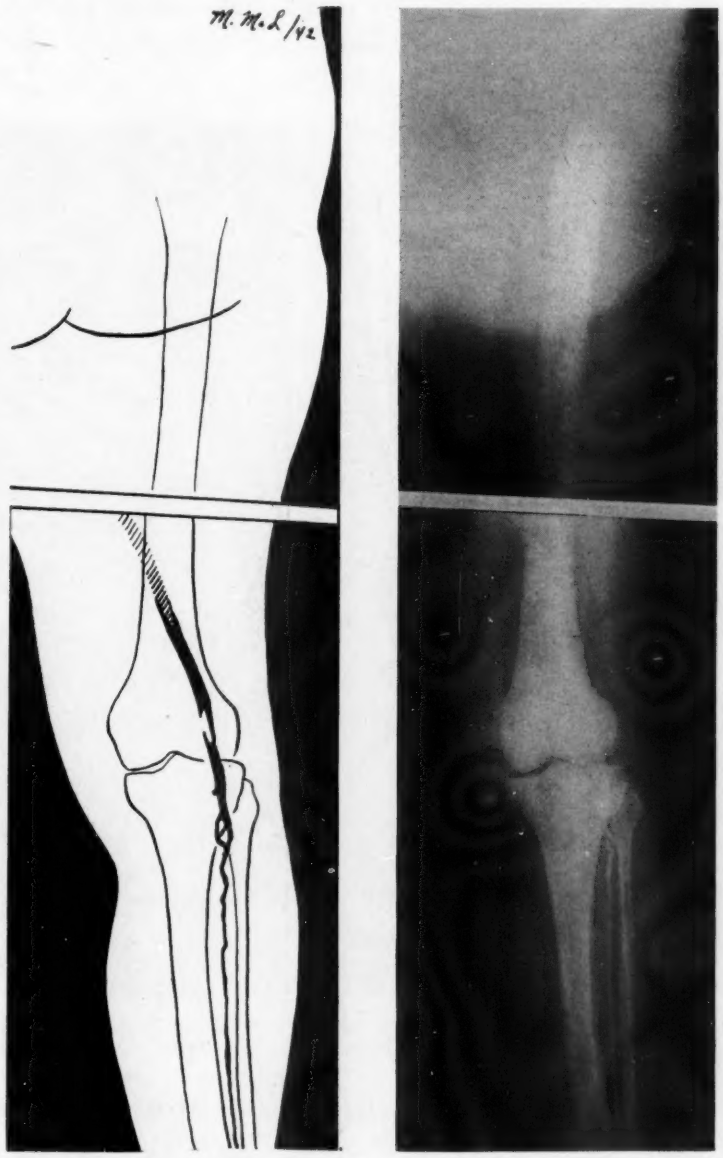

Fig. 8.—T. I. (M. G. H. No. 319658). Early deep phlebitis of the lower leg. No filling of the posterior tibial vein. The upper femoral vein was not visualized because of an insufficient amount of diodrast.

In this group, the thrombosis has been recognized at an early stage. The superficial femoral vein may be ligated and the patient may be allowed out of bed at once with no fear of embolism.

(c) The popliteal and lower femoral veins are partially thrombosed. This is a stage intermediate between (b) and (a). Occasionally a loose

thrombus in the femoral vein is actually demonstrated by the diodrast passing around the thrombus. This has aptly been termed by Bauer "mantle filling." In this group of cases a loose clot can usually be withdrawn from the femoral vein. Embolic phenomena are especially common, are apt to be fatal, and can be prevented only by ligation of the vein.

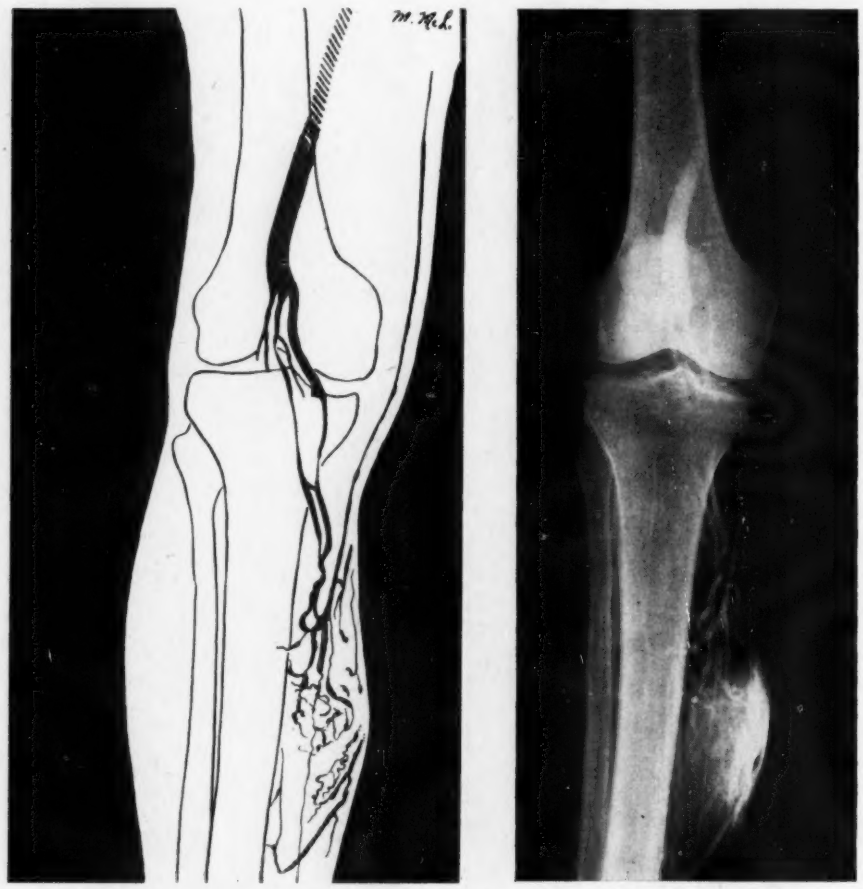

Fig. 9.—P. B. (M. G. H. No. 329354). Acute deep thrombophlebitis confined to the veins of the lower leg. Diodrast is seen in only the superficial veins and uppermost portion of the crural veins.

L. H. (M. G. H. No. 243171), a 39-year-old male, developed tenderness and pain in his left calf three days after drainage of a lung abscess. The calf was moderately swollen. His phlebogram (Fig. 10) showed incomplete block of the popliteal and femoral veins and demonstrated the escape of the diodrast along the periphery of an eel-like thrombus. Immediate exploration yielded a large, soft clot lying free in the common femoral, the head of which was recovered from the external iliac by introducing the Trendelenberg suction tip. The common femoral and sapehnous veins were ligated and divided. Recovery was uneventful. Four months later, in the outpatient department, no swelling of the leg was demonstrated.

(d) Occasionally, the entire femorocrural system will not be found to be thrombosed, but mural thrombi involving only a portion of the fem-

oral vein will be observed. If a long saphenous phlebitis is present, this indicates that the thrombosis has extended by way of the communicating veins from the saphenous to the femoral vein. Such patients are especially prone to repeated attacks of small pulmonary emboli.

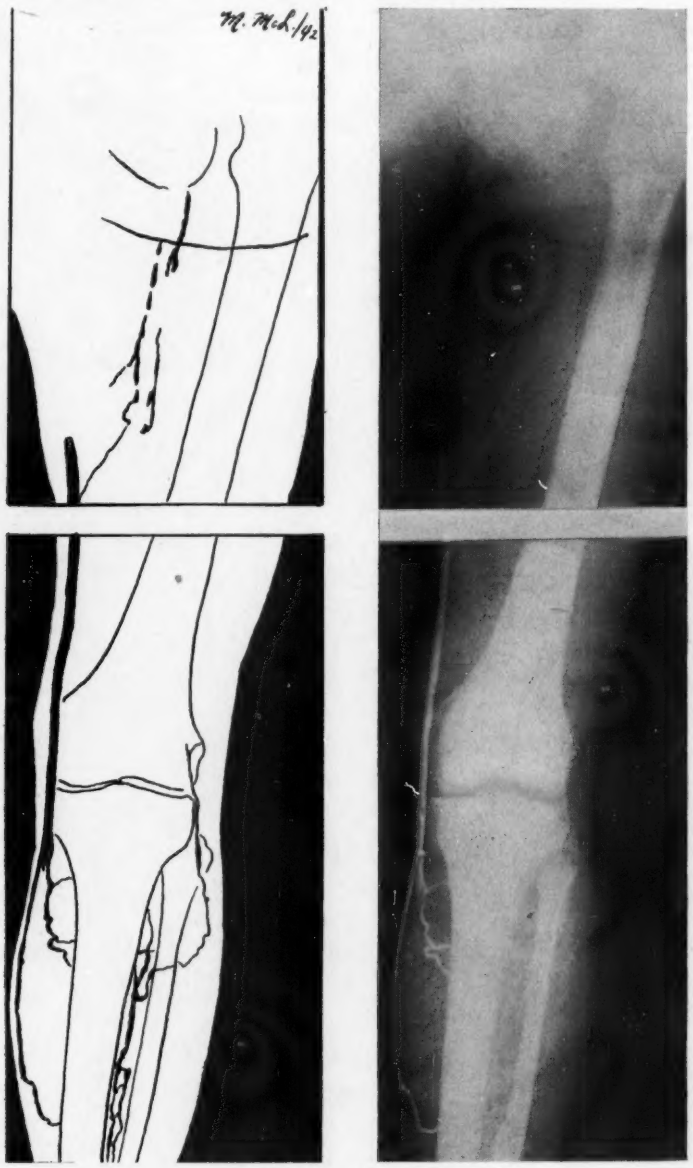

Fig. 10.—L. H. (M. G. H. No. 243171). Mantle filling showing the diodrast escaping along an incompletely fixed thrombus in the upper femoral vein.

Very rarely the phlebogram of the lower leg and popliteal veins may appear normal, with a large, loosely-attached thrombus in the femoral vein. This is an important type, from a theoretical point of view, since it proves that massive thrombosis of the crural veins does not always precede thrombosis of the femoral vein. These thrombi are floating in a

rapidly moving column of blood, and are the most dangerous type of all. Immediate ligation is essential to prevent death from a massive embolus.

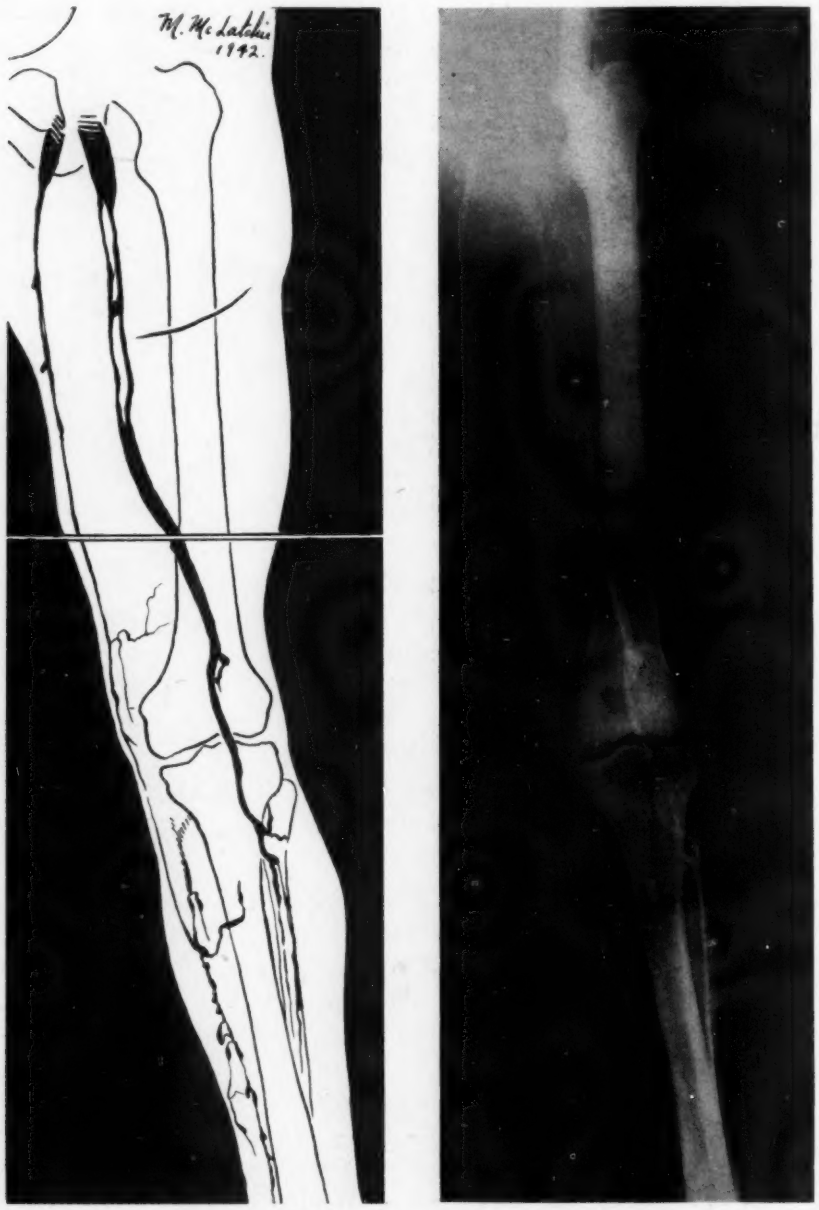

Fig. 11.—A. C. (M. G. H. No. 304502). Mural thrombus seen in the middle and upper portions of the femoral vein. Note deep system filling below.

A. C. (M. G. H. No. 304502), a 56-year-old female, was operated upon Jan. 27, 1942, for a Dupuytren's contracture of the left hand. She was allowed to be out of bed for the first three postoperative days. The following day her temperature rose to 100° F. and twenty-four hours later she developed pleuritic pain over the right chest and a nonproductive cough. Chest x-ray showed a high right diaphragm with linear atelectasis. During the next five days in bed the chest pain disappeared

and her fever lessened. After being up again for two days she had a return of the chest pain with fever to 100.6° F. Chest x-ray showed multiple small areas of pulmonary infarction over both lower lung fields. For the first time her left calf and ankle measurements were one-half to three-fourths of an inch greater than the right. No areas of tenderness were elicited, but the patient complained of a mild ache in the calf. Bilateral phlebograms were made showing normal filling on the right. In the upper femoral region on the left was a large mural thrombus (Fig. 11). Immediate femoral exploration confirmed this finding and a large, soft clot was aspirated from the distal segment of the femoral vein. The patient's course was subsequently uneventful.

THERAPY

The therapy of venous thrombosis will be considered only briefly. In our clinic we have attempted to evaluate venous ligations, chiefly because our incidence of emboli has been high. Thus, our control group showed one infarct out of every three cases of deep phlebitis, while the death rate of thrombo-phlebitis in patients over the age of 50 was nearly 8 per cent because of massive infarcts alone.[7] The mechanical prevention of emboli by actual ligation was, therefore, especially appealing.

We have now ligated eighty-two femoral veins for deep venous thrombosis. Ligation is done in any case if the patient is 40 years of age or over, or if he is under 40 and has a bland thrombosis or has had a pulmonary infarct. Of the patients in the ligated group, the average age was 56. According to our control figures we should have expected that about twenty-five patients would have had further pulmonary infarcts, while six would have been fatal in this group if conservative therapy had been employed. However, after ligation we observed only two infarcts, one of which could not be confirmed by x-ray, and neither one of which was fatal. Bilateral ligations have been done nine times.

The site of ligation is very important and may be determined by the phlebogram. The vein should be ligated below a large branch in order to avoid a long static column of blood with potential thrombosis and fatal embolism. This means that ligation of the popliteal vein should not be done. Ligatures may be placed on the superficial femoral, common femoral, or iliac vessels. Since most of these operations are done in very ill patients, we have tended to make the procedure as simple as possible and have avoided the extra dissection required for iliac ligation, preferring to use suction to withdraw thrombi from higher levels. Practically, then, the decision must be made as to whether to ligate the femoral vein below the profunda branch, above the saphenous junction, or at some point between. It is advisable to ligate above the thrombosis if possible. If not, the vein must be opened over the thrombus and the clot extracted with a suction apparatus.

In certain cases the venous anastomosis above and below the site of ligation is poor. This had led in two cases to marked distention of the entire venous system of the extremity and to extravasation of blood into

the wound. This very serious complication occurred in both cases when the ligature was placed above a patent profunda femoris. We believe that if the superficial femoral vein had been ligated instead, the venous anastomosis would have been adequate and these catastrophes prevented. Therefore, if the thrombosis in the femoral vein does not extend beyond the mouth of the profunda the superficial femoral vein is chosen for the ligation.

If the long saphenous vein is not thrombosed or varicose in type and it is well delineated by the dye in the phlebogram, it is certain that the ligation can be done below the saphenous vein and usually below the profunda. On the other hand, if the long saphenous vein is involved in the thrombosis, it is necessary to make the incision higher and ligate above the sapheno-femoral junction.

As has been previously emphasized, it is important to open the vein before ligating it, in order to prevent section of a free-lying thrombus by the ligature.

SUMMARY

The members of the Peripheral Vascular Clinic, under Dr. Leland S. McKittrick, have summarized the various procedures indicated in this group of cases for the benefit of the resident staff, who prepare the phlebograms and perform the majority of the ligations. These conclusions are not presented as final dicta, but as a practical guide in the present state of our knowledge.

THERAPY OF THROMBO-EMBOLISM

Patients in whom thrombophlebitis of veins of the lower extremity is suspected or who have had a pulmonary embolus must have the following procedures carried out.

1. Phlebogram: A blood-pressure tourniquet is placed about the mid-calf and inflated to 20 mm. of mercury. 25 c.c. of diodrast is injected into a dorsal vein of the foot or the distal long saphenous vein. The injection should take one minute; exposure is taken at the exact conclusion of the injection.

2. Alternate Method: If, because of sepsis or for other reasons, these veins are not available, the short saphenous vein may be isolated after novocain infiltration behind the external malleolus and injection carried out in a similar fashion.

The manner in which the phlebogram is taken should be noted on the record.

3. The circumference of both legs and thigh at various intervals should be recorded before therapy, and at three-day intervals thereafter. These measurements should be recorded as:

> 12″ above top of patella; 6″ above top of patella; 6″ below top of patella; 12″ below top of patella; maximum lower leg.

4. In addition, the pressure or absence of Homans' sign and of tenderness in the calf should be noted.

It is recommended that venous ligation be done in the following manner:

A. Site.

1. If there is a free superficial femoral vein and the long saphenous vein is not involved and not varicose in type, the ligation is done just below the profunda femoris. This vein is usually found 5 cm. distal to the sapheno-femoral junction.

2. If the superficial femoral vein is thrombosed, the common femoral vein is explored at the level of the sapheno-femoral junction. Proximal and distal thrombi are removed in this order by suction. The femoral and saphenous veins are ligated.

3. If the saphenous vein is varicose in type, and the superficial femoral vein is free of thrombus, the saphenous vein should be ligated at the sapheno-femoral junction and the superficial femoral ligated below the profunda femoris.

B. Type of Ligation.

1. Ligation in continuity should not be done until the surgeon has assured himself, by actually opening the vein, that no thrombus is present at the site of ligation.

2. The vein, thereafter, may either be ligated doubly in continuity, or ligated doubly and divided. The type of suture material must be noted in the record.

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THROMBOSIS OF THE AXILLARY VEIN

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THROMBOSIS of the axillary vein is not a common condition. It is usually associated with indirect trauma in the form of a sprain or strain. The symptoms are identical with thrombophlebitis of the lower extremities except that local and constitutional signs of an inflammatory process are absent. Unlike thrombosis in the lower extremities, it does not follow operations. It is not associated with debilitating conditions nor does it often occur in association with cardiac decompensation. It rarely develops after direct injury to the extremity and rarely complicates blood dyscrasias in which thrombosis are wont to occur.

The literature on the subject is not abundant. Cases are reported occasionally, but no great number by any one observer. The most thorough review of this condition was made by Matas, in 1934, while reporting a case.[1] In his discussion he included diagnosis, pathogenesis, and treatment, as well as medicolegal aspects. However, in reviewing all cases to date one is impressed with the part that trauma plays, varying in degrees from slight to severe. A study of the cases showed the condition to develop in young healthy individuals and to involve the right arm most frequently. When the left arm was involved an undue strain was placed upon it. Males were preponderant in the series but the syndrome was also noted in females. It followed such diverse efforts as those associated with grinding a spark plug, stirring clothes while washing, pulling oneself up by holding on to the head of the bed, checking and restraining a horse, swinging at a golf ball, pitching a baseball, lifting a heavy pressing iron, lifting a cake of ice, lifting a storage battery out of a car, and putting books on a shelf. In rare cases thrombosis developed during sleep without any antecedent history of strain or sprain.

The onset is usually acute but may also be gradual. Pain experienced in the entire arm is followed by swelling and cyanosis which may require several hours or days to develop after the strain. Because of an associated arterial spasm the hand may be colder than that of the uninvolved side and the peripheral pulses may be of smaller volume.

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In no case, however, has there been such degree of spasm as might produce gangrene of the digits, which sometimes happens with thrombosis of the femoral vein where there is an associated spasm of the femoral artery.[2] A tender cord can be felt on the inner side of the arm over the brachial vein, continuing upward to the axillary vein.

After a period of time ranging from a few days to several weeks, the edema subsides and superficial veins and venules appear over the arm, anterior chest wall, and axilla. The venous pressure is increased and the circulation time prolonged. The veins in the antecubital region do not collapse completely when the arm is held above the heart level. Injection of an opaque dye into the veins about the elbow region reveals new collateral formation, dilatation and distension of veins, irregular course and distribution of the dye through vessels not normally visualized, and evidence of stasis. Photographs taken with infrared technique show numerous superficial veins not normally seen.

Several theories have been advanced for the development of this syndrome. Von Schrotter[3] who first described the entity in 1884, maintained that the stretching of the muscle stretched the axillary vein and caused a localized phlebitis resulting in thrombosis. Cadenat[4] believed that the respiratory effort that was associated with strain distended the vein and produced a change in the intimal lining of the vessel leading to thrombosis. Lowenstein[5] contended that holding the arm in the abducted position distended the axillary vein and caused the costocoracoid ligament and subclavius muscle to indent it. This distention plus pressure upon the vein was sufficient to produce thrombosis. Gould and Patey[6] confirmed these findings, but in addition, demonstrated a valve present at the level of the subclavius muscle which ruptured following pressure by the muscle on the axillary vein. This, they advanced as the fundamental cause of the thrombosis. Veal and McFetridge,[7] on the other hand, held that the thrombosis was due to a compression of the vein below the head of the humerus against the subscapularis muscle. These theories were advanced to explain cases of thrombosis with a history of severe trauma or unusual strain; they do not clarify cases of thrombosis appearing during sleep where there has been no reported trauma or cases where trauma is slight or absent. When thrombosis develops during sleep it is probably caused by a prolonged compression of the vein induced by the position of the arm, particularly when it is elevated over the head or folded under the body. The venous blood flow becomes obstructed and one of two things happens: either the lowered oxygen content of the blood resulting from the obstruction to its flow produces a change in the intimal lining thus forming the basis of the clot, or changes are produced in the constricted region whereby the intima is damaged by direct compression causing thrombosis.[8]

Concerning infection as a causative factor one should note the absence of a temperature rise, both local and general, the absence of the usual history of a chill as is found with thrombosis in the lower extremities, and absence of other evidences of toxemia as well as the presence of a normal blood picture. According to a careful study of the literature there are no blood diseases that predispose to axillary thrombosis.

The role played by the sympathetic nervous system has been emphasized by Cottalorda[1] who believed that the trauma irritated the sympathetic plexus, induced vasospasm and terminated in a vascular lesion. Associated with the venospasm is a thrombosis of the vein which appears clinically as an edema of the arm. Disappearance of the edema and correction of the vasomotor imbalance follow the excision of the involved venous segment.

Similarly, Ochsner and DeBakey[9] find that vasospasm is a greater factor in producing the clinical manifestations of thrombophlebitis than the thrombus itself.

Thrombosis of the axillary vein should be differentiated from arteriovenous aneurysm. In the former, the oxygen content of the venous blood is low, the temperature of the extremity is normal or subnormal, arterial pulsations are present and are of normal volume, and a thrill and bruit are absent. In the arteriovenous aneurysm the oxygen content of blood from a vein of the extremity is high, the temperature of the extremity is increased, the arterial pulsations are diminished or absent, and a thrill is felt and a bruit heard.

Following herewith are reports of three cases of axillary vein thrombosis, one in a female and two in males, who at the time were in good health with no discernible background to explain the occurrence except trauma.

CASE 1.—S. R., female, aged 62 years, whose occupation was that of clipper of horses' hair, was admitted to the hospital Oct. 7, 1939, because of an enlargement of the right arm and distention of the veins over the right upper extremity, axilla, and pectoral region. This enlargement and distention were of twenty-six years' duration. Patient could not remember any history of acute edema of the arm and claimed to have always been in moderately good health. There was no history of cardiac embarrassment or dyspnea.

General physical examination revealed a well-built and well-nourished female in whom no other findings that could bear on this condition were present. A mild hypertension of 170/90 was found.

The right upper extremity was larger than the left and the veins over the right upper extremity, axilla, and anterior chest wall were dilated, tortuous, and more numerous than those of the left. The veins of the right arm collapsed on elevation but more slowly than of the left. There were no evidences of palmar ischemia on elevation nor of dependent rubor. The brachial, radial, and ulnar arteries of both extremities were of equal volume and the temperature of both extremities, the same. No cord or thrill could be felt in the axilla, nor was a bruit heard.

Blood examination revealed a normal cell count and no blood dyscrasias. The blood Wassermann test and chemistry were normal. Venous pressure in the right basilic vein was 130 mm. and in the left 110 mm.

Roentgenograms of the chest failed to reveal evidences of aneurysms or intrathoracic masses to account for pressure or interference with the return circulation.

Injection of 10 c.c. of diodrast into the cephalic vein showed it to be dilated and tortuous, and to cross over the head of the humerus, continuing in the same pattern over the chest wall. Collaterals were seen in the supraclavicular and cervical regions. A collateral from the cephalic vein crossed the humerus below the neck to empty into the site of the axillary vein. The axillary vein was not visualized and the cephalic vein did not empty into it. A second exposure taken immediately after the first revealed the dye to be present in spots in the cephalic vein. The tortuous vessels over the thoracic cage as well as the collaterals in the supraclavicular and cervical regions were no longer present.

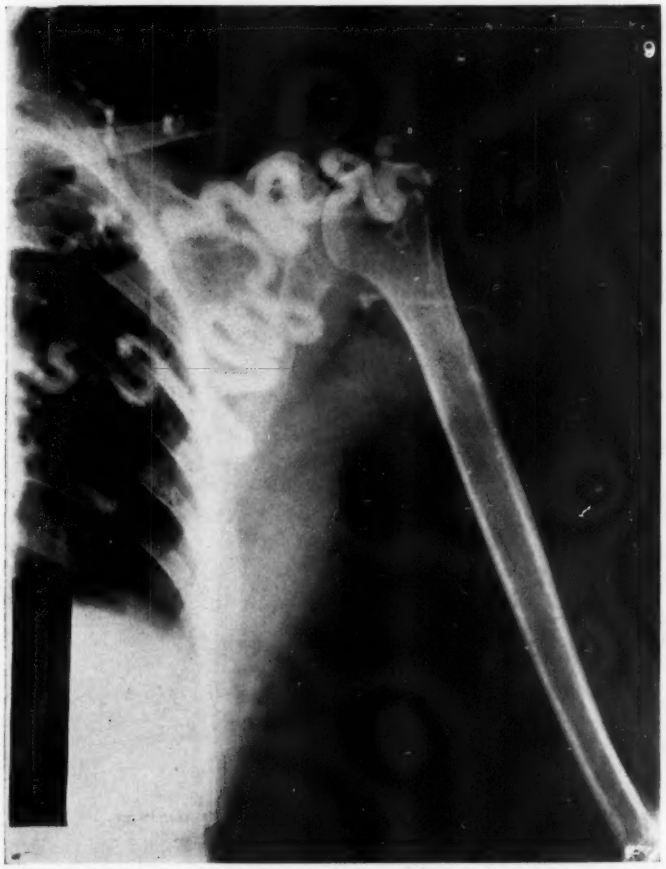

Fig. 1 (Case 1).—Injection of 10 c.c. of diodrast into the cephalic vein reveals the vein to be dilated, tortuous, and continuing in that pattern over the thoracic cage. Collaterals are seen in the supraclavicular and cervical regions. A collateral coming off the cephalic vein crosses the humerus below the neck, emptying into what should be the site of the axillary vein. The cephalic vein per se doesn't empty into the axillary vein.

Comment.—The report just cited is a case of thrombosis of the axillary vein associated with the occupation of hair clipping on horses in which the arm was constantly held in the outstretched and abducted position.

CASE 2.—P. B., a white male, aged 23 years, helper on a truck, on June 7, 1939, lifted a case of milk weighing sixty pounds from a platform onto a truck. As he lifted the case he felt a sudden pain in the left arm. The arm subsequently became stiff and swollen. Within four hours the entire left upper extremity became so swollen that he had to support it with his right hand. Several days later, as the swelling decreased, he noticed numerous prominent veins over the arm. The hand was heavy and discolored.

Examination Aug. 29, 1939, revealed a well-nourished male in whom all physical findings were negative. The laboratory data bore no significant relation to the local condition. The veins over the left upper extremity in the axilla and over the chest wall were more numerous and dilated than those on the right side. The veins in the left antecubital region collapsed more slowly on elevation above the heart level than did those on the right. The brachial, radial, and ulnar pulsations could be felt and were of good volume. There was no bruit or thrill. The left hand was slightly colder than the right and the hand grasp, weaker. A tender cord was present in the axilla.

The left arm was larger than the right, the exact comparative measurements being as follows:

	RIGHT	LEFT	DIFFERENCE
Junction of shoulder and arm	31 cm.	32 cm.	1 cm.
Mid-arm	27 cm.	28 cm.	1 cm.
Elbow	24½ cm.	26½ cm.	2 cm.
Wrist	16½ cm.	18 cm.	1½ cm.

Circulation time using 10 per cent calcium gluconate was computed at twenty-five seconds in the left arm and ten seconds in the right. The venous pressure in the left basilic vein was 210 mm. of water as compared with 90 mm. of water in the right basilic vein.

Radiographs of the left shoulder region failed to reveal any evidence of bone or joint pathology and radiographs of the thoracic cage revealed no evidence of tumor or masses.

Treatment consisted of the application of an elastic bandage spirally from the palm up to the axilla, enabling the patient to resume his duties.

Re-examination three months later revealed the left upper extremity still larger than the right. The veins had not receded in size or number. The mass in the axilla, previously tender, was no longer felt. The antecubital veins still collapsed slowly upon elevation.

Comment.—The case described is one of axillary vein thrombosis which followed a severe and sudden sprain associated with the lifting of a weight of sixty pounds.

CASE 3.—J. K., a white male, aged 27 years, employed as a shipping clerk, on March 10, 1939, pulled and pushed a silk-measuring machine weighing 250-300 pounds. He felt a sudden shock-like pain in the left arm. About one-half hour later the hand became swollen and blue. A day later the entire left upper extremity became swollen and hard and a painful mass was felt in the axilla.

Examination March 26, 1939, revealed the left upper extremity enlarged and of a dusky discoloration with numerous superficial veins and venules over the left arm, left anterior pectoral and axillary regions. The lateral thoracic vein was prominent. Veins in the elbow as well as those on the dorsum of the left hand were very distended. There was no clubbing of the fingers and motion in the joints was unimpaired. A tender cord was felt in the left axilla.

Comparative measurements were as follows:

	RIGHT	LEFT	DIFFERENCE
Junction of humerus and shoulder	28½ cm.	30½ cm.	2 cm.
Mid-humeral	28½ cm.	30 cm.	1½ cm.
Elbow	25½ cm.	26 cm.	½ cm.
Mid-forearm	26 cm.	26¾ cm.	¾ cm.
Wrist	17¾ cm.	18 cm.	¼ cm.
Palm	20½ cm.	21 cm.	½ cm.

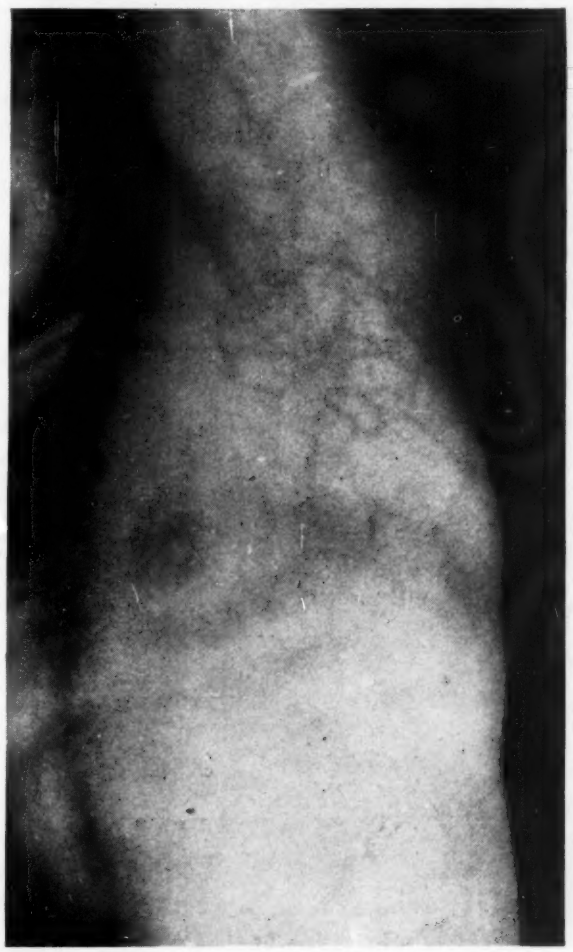

Fig. 2 (Case 3).—Infra-red photography reveals numerous superficial veins in the left axilla and on the under surface of the upper arm.

Upon elevation of both extremities above the heart level the veins of the right upper extremity collapsed readily, whereas those of the left were slow, some not collapsing at all. The arterial circulation was not impaired, the oscillometric reading over the left brachial artery being seven, and over the right, nine. This difference was probably due to a spasm associated with the venous thrombosis. The left hand was colder than the right. Circulation time with calcium gluconate was twenty-one seconds as compared with a normal of ten to twelve seconds. Venous pressure was 410 mm. of water as compared with a normal of 60 to 120 mm.

X-rays of the thoracic cage failed to reveal any evidence of masses or growths to account for obstruction. Infra-red photographs showed numerous superficial veins over the left arm and in the left axilla.

Re-examination June 14, 1939, revealed the left upper extremity still enlarged and of a dusky discoloration. There was no restriction in mobility of the joints. The venous pattern previously described had not changed. The cord in the axilla which was tender when first examined was still present, although no longer tender. Circulation time was still twenty-one seconds and venous pressure had decreased from 410 mm. to 380 mm. of water.

Subsequent examinations revealed the extremity still enlarged with the veins distended.

Comment.—The above is a case of thrombosis of the axillary vein following the undue strain of pushing and pulling a 250-300 pound machine.

DIAGNOSIS

A diagnosis of thrombosis of the axillary vein can be made from (1) a history of trauma which may vary in intensity from slight to severe, (2) swelling and enlargement of the extremity, (3) prominence of the existing veins and appearance of new collateral veins and venules, (4) distension and failure of the veins to collapse completely and readily when the extremity is elevated above the heart level, (5) increase in the circulation time, (6) increase in the venous pressure, (7) visualization by means of the injection of an opaque medium of new collaterals, dilatation and distension of veins, and stasis, (8) increase in the number of superficial veins as shown in photographs taken with infra-red technique.

TREATMENT

The traditional treatment for axillary thrombosis in the acute stage is rest to the part, elevation, and local application of hot, moist packs. When the edema subsides, an Ace bandage extending spirally from palm to shoulder is applied until a new collateral circulation develops.

On the basis of the part played by the sympathetic nervous system in thrombophlebitis, however, Ochsner and DeBakey[10] advocate the infiltration of novocain or procaine into the corresponding lumbar and cervicodorsal sympathetic ganglia. They have used this method with success in cases of thrombophlebitis of the extremities, complete relief from pain and disappearance of the edema having followed interruption of the sympathetic reflexes. This form of therapy avoids the drastic approach of Cottalorda,[1] namely thrombectomy and excision of the affected segment, and thus has the obvious advantages of conservative treatment.

Activity is resumed gradually with the possibility of recurrence kept in mind.

PROGNOSIS

The duration of the edema and swelling is variable and severity of the residual symptoms depends on the extent of the new collateral venous

circulation established. Following prolonged use, the patient may feel a sense of heaviness, fullness, fatigue, or cramps in the extremity. In some cases there may be recurrence of the edema following exertion. No deaths from embolism have been reported.

SUMMARY

1. Three cases of axillary vein thrombosis have been described, one in a female in which the right arm was involved and two in males in whom the left arm was involved.

2. The theories as to its formation have been reviewed briefly.

3. The findings helpful in diagnosis have been enumerated.

4. A brief résumé of the treatment and prognosis has also been included.

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A REVIEW OF STUDIES ON WATER AND ELECTROLYTE BALANCE IN SURGICAL PATIENTS

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THE chief characteristic of medicine in this country has always been originality of thought combined with a sturdy independence of action. It may have been a fortunate deprivation that there were no medical schools here for more than one hundred and fifty years after the first settlements were established. Such medical schools as existed abroad were shackled by ropes of convention and bonds of authority while in this new country the sick were treated by men brought up in the apprentice system where academic fixation was lacking and initiative was untrammeled. Only five medical schools had been established before 1800, designed to supplement the apprentice system of training but accomplishing it in a formal, sterile manner. By this time the great migration of population to the west was well under way, to continue for more than a century. With the waves of pioneers went their doctors, who worked alone, without opportunity for consultation or formalized study. These men were forced to solve the many problems of practice through their own ingenuity and originality.

It was in this environment and because of it that American medicine first began to make significant additions to medical progress. McDowell, Beaumont, Crawford, Sims, Drake and others made their contributions under these circumstances of isolation, with freedom for unorthodox and unfettered activity. With the mass movement of people to the West came a corresponding expansion of medicine. Literally hundreds of medical schools were established, most of them without facilities but the right to collect fees and to grant diplomas. A majority of the graduates of these schools were better than the sources of their training, and medicine improved through the impetus of men rather than from that of their schools. We are familiar with the sweeping changes that have taken place in medical education in the last generation. Medical schools have assumed university stature and have become centers for the nuture of genius and of intellectual curiosity. Medicine has now become cooperative while still fostering individualism.

We have met tonight to honor one of the last of the group of pioneer individualists who bridged the gap from the old to the new.

The last of the many important contributions of the frontier physician to medicine was the development of the idea of cooperative practice in the small Minnesota town where Edward Starr Judd lived and worked. A

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man of shyness and of self-effacing modesty he would not wish to have either his personality or his achievements discussed, much less praised. He must not mind, however, if we say that he was one of the last of that group of men in American medicine who gave us our national medical character and who brought to it the initiative, honesty, and originality of the pioneer and contributed vastly to the collective knowledge of today.

A master surgeon of all time, his interests were manifold but he was truly a pioneer in joining to the anatomic and pathologic aspects of surgery an interest in the physiologic. In emphasizing this point I will attempt to discuss a subject that might well have interested him, since it deals with the well-being of the sick, that is, some of the abnormal chemical changes encountered in surgical patients.

A complete review of the historical side of this subject would necessitate reference to much of the basic work in chemistry and physiology, which is clearly impossible, but a few of the landmarks may be mentioned. Sanctorius Sanctorius,[32] the "first famous master of experimental medicine," published his *Ars de Statica Medicina,* in 1614, in which he tells of his observations with the thermometer, pulsilogium, and the balance. His aphorisms dealing with insensible perspiration are of particular interest since the phrase is his. In Aphorism II he states, "If a physician who has the care of another's health is acquainted only with the sensible supplies and evacuations and knows nothing of the waste that is daily made by insensible perspiration, he will only deceive his patient and never cure him."

Other men studied insensible perspiration, one of the most interesting of whom was Dr. John Lining of Charleston, South Carolina, who throughout all seasons of the year 1740, carried on observations on himself concerning loss of weight through perspiration. He hoped that these studies made in a climate subject to violent changes might throw light on "the nature and predisponent causes of epidemic diseases."

Many studies of insensible perspiration have been made since, particularly by Lavoisier, who demarked cutaneous respiration from pulmonary respiration up to the definitive investigations of Benedict and Root,[3] in 1926, that showed that the insensible loss varies with the rate of metabolism.

We now know that the maintenance of water and electrolyte content of the body is important but it is interesting to read the short communication written to the London Medical Gazette, in 1831, by Dr. W. B. O'Shaughnessy of Newcastle-on-Tyne about his observations on patients with cholera.[27] In it he stated:

> 1. The blood drawn in the worst cases of the cholera is unchanged in its anatomical or globular structure.
>
> 2. It has lost a large proportion of its water, 1,000 parts of cholera serum having but the average of 850 parts of water.
>
> 3. It has lost also a great proportion of its neutral saline ingredients.

4. Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.

5. Urea exists in the cases where suppression of urine has been a marked symptom.

6. All the salts deficient in the blood, especially the alkali or carbonate of soda, are present in large quantities in the peculiar white dejected matters.

He then states that cure is seemingly dependent upon two principles: "First, to restore the blood to its natural specific growth (i.e. its water content); second, to restore its deficient saline matters." He goes on to state that "the first of these can only be effected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks with sufficiently obvious modifications, apply to the second." He recommends for practical therapy, "in severer cases, copious enemata of warm water, holding the natural salts of the blood in solution. . . . When absorption is entirely suspended, the author recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood." These brilliant observations carried on 110 years ago with meager facilities and methods show clearly that dehydration and salt depletion are serious factors in cholera.

The German chemist Karl Schmidt confirmed the truth of these statements and amplified them by improved technical methods. Dr. C. Hilton Fagge reported from Guys Hospital, in 1874, "A case of diabetic coma treated with partial success by the injection of a saline solution into the blood." The reason for its use was given by him as follows: "What suggested to my mind the advisability of injecting a saline solution into the blood in this case was the idea that coma was due to the drain of water from the system, caused by diabetes. I suppose that the hypothesis upon which I acted was essentially similar to that which formed the basis of the like treatment in the collapse of cholera." But saline solutions were little used in therapy until the beginning of the twentieth century.

The use of salt solutions received its real impetus after the reports by Rogers, and Nichols and Andrews in 1909, of its efficacy as therapy in the treatment of cholera during an epidemic of that disease in the Philippine Islands. The use of saline solution in surgery was slowly adopted. At first it was usually given as a retention enema. Later it was given as a rectal drip after the popularization of this method by J. B. Murphy. In 1912, Hartwell and Hoguet showed that, after complete obstruction of the lower duodenum in animals, life could be greatly prolonged by the daily subcutaneous administration of normal salt solution in amounts slightly in excess of the total volume of the urine and vomitus of the previous twenty-four-hour period. They concluded that the effect was due to a relief of dehydration usually present to a marked degree in high intestinal obstruction.

In 1914, Tileston and Comfort observed the rise in blood nonprotein nitrogen that accompanies the dehydration of high intestinal obstruction,

this observation being confirmed by Cooke, Rodenbaugh, and Whipple, in 1916. In 1918, McCann described the alkalosis which occurs from loss of stomach secretions associated with pyloric obstruction. In 1920, MacCallum and his associates described the fall in plasma chloride concentration after the pylorus was obstructed. They also showed that the giving of sodium chloride prevented both the fall in plasma chlorides and the rise in the carbon dioxide combining power of the plasma, and that the administration of either hydrochloric acid or sodium bicarbonate prevented neither. Haden and Orr, in a series of important studies on the altered chemistry associated with intestinal obstruction, emphasized that azotemia, hypochloremia and alkalosis are present in high intestinal obstruction. They corroborated the findings of Hartwell and Hoguet on the beneficial effects of the giving of saline solution and demonstrated that many salts of sodium, and of chlorine other than sodium chloride, may be ineffective. They showed that water alone does not prevent the onset of symptoms and death from high intestinal obstruction as had been postulated by Hartwell and Hoguet. Many investigators in the laboratory and the ward have substantiated and continued these studies and one can only mention the names of a few for lack of space. Important and basic contributions have been made by Gamble, Gatch, Hartmann, Peters, Darrow, and many others to put this whole aspect of disease upon firm scientific foundations.

From this accumulated knowledge built up by many investigators it has become clear to the clinician that the deprivation of, or loss of, water and electrolytes from the body through disease or treatment will give rise to untoward symptoms and may be the cause of death. Physicians have long recognized the truth of these observations and fluids of many sorts have been given to sick patients in many ways.

Some years ago it was clear to us that in our surgical wards we were giving fluids to patients in a more or less haphazard way and we began to study these problems in a quantitative manner in the hope that we might develop facts that would enable us to have simpler working rules for the accurate replacement of water and electrolytes when they were needed. I propose to give a brief summary of the various studies made over the past eight years, knowing, however, that many of you are already all too familiar with them.

The animal life of the ocean that adopted a terrestrial life could not free itself from the sea and therefore had to carry the sea with it as extracellular fluid. As a consequence, it added the tremendous task of maintaining the constancy of that infinitesimal portion of the ocean that it contained within its corporeal limits to the already highly complex task of regulating internal environment. This task is more or less successfully performed by the normal animal with the adaption of varied and more or less efficient physiologic expedients, principally the skin and glomeruli.

The human being in the light of comparative physiologic knowledge is in some ways inferior to many of the so-called lower forms of life. Especially is this true in his relative lack of safeguards for the maintenance of the constancy of body fluids under adverse environmental conditions. For instance, during hot weather, man regulates his body temperature by excreting as sweat, a dilute salt solution, yet he experiences no salt hunger even though the loss of salt may cause his death. However, the dog, the ass, and the ox under like circumstances are spared a similar fate; the dog and the ass[9] because they do not lose salt in significant quantities with the water vaporized, the ox because, although he sweats a weak salt solution, develops salt hunger as the sodium chloride of the body is depleted and will therefore make a supreme effort to get the needed salt. The physiologist knowing only the working of the heat regulating mechanisms of the ass could die of salt depletion from sweating, drinking water and swearing until the end that he could not be dying of lack of salt because the amount of salt lost in sweat was insignificant; and he who knew only the physiology of the ox would die with the salt before him while he awaited the sensation of salt hunger to urge him to take it. It is therefore obvious that the ultimate basis for the establishment of practical principles for regulating the salt and fluid balance of an ill man must come from experimental work done on man. Furthermore, it would be likewise hazardous to set up those principles upon the basis of knowledge gained from acute experiments on normal man because the basic fluid and salt requirements are affected, for instance, by the metabolic rate,[3, 24] the blood and lymph loss during the operation, the rate of loss in exudates, and through the enteric, biliary, pancreatic, and lymphatic fistulae. Therefore, it was realized that although a great mass of knowledge concerning salt and water metabolism was available it could not be intelligently employed in surgery until the specific requirements of man suffering the varied ills that are treated surgically were known. It has been largely toward that end that the major part of the work done on water and salt balance at the University of Michigan has been directed.

It was realized when the problem was first undertaken that a basic approach to the problem required that the water needs of the surgical patient be known; that necessitated the establishment of the amounts of water and salt required by the relatively normal individual under the conditions to which a patient would be subjected during and after a surgical procedure. The factors that had to be taken into account were insensible loss of water, the water necessary to excrete body wastes without having the kidney concentrate the urine to its limit of capacity, the water lost in stool, and the water lost by sweating. The insensible loss of water from skin and lungs amounts in the average adult to about 1,200 c.c. each twenty-four hours.[3] This amount increases as metabolic rate increases and as breathing in-

creases;[3, 5, 25] allowance, therefore, should be approximately made. From direct determinations on surgical patients it was concluded that the insensible loss could usually be covered by 1,000 c.c. in small inactive individuals and by 1,500 c.c. in the larger or more active.[6] The water necessary to excrete the average amount of waste formed in the body daily (35 Gm.) amounts to about 500 c.c. of water with the normal kidney concentrating near capacity (specific gravity, 1.030).[16] The insufficient kidney requires more water to excrete 35 Gm. of waste, therefore, to have an adequate margin of safety requires that 1,000 c.c. be considered the minimum urine excretion in the surgical patient.[6] The water lost normally in the stool is small, 100 c.c. daily; that lost by sweating varies with the season, the temperature of the operating room, the extent of draping, and the type of covering of the individual before full reaction from the anesthesia has occurred. During the hot, humid weather of a Michigan summer, without air conditioning either in the ward or operating room, as much as 4,000 c.c. of sweat was lost in a single twenty-four-hour period by a patient quietly lying in bed.[36] It was concluded, therefore, that an uncomplicated surgical case, not perspiring, requires from 2,000 to 2,500 c.c. of water daily. Due allowance must be made from the increased requirements incident to fever, hyperthyroidism, and sweating. In general, under these conditions 3,000 to 3,500 c.c. are required.[6]

Beside the water needed to keep the body water within normal limits of composition and amount, provision must be made for the replacement of the salts lost. In contrast with the relatively large amounts of water that must be excreted daily, the body is capable of conserving certain electrolytes when the intake is insufficient so that a normal nonsweating person will excrete only traces of chloride in the urine[2, 22] (0.1 Gm. per twenty-four hours)[6] when there is no excess intake. The administration of 5 Gm. of salt therefore provides more than adequately for normal needs.[6] The concentration of salt in sweat varies widely in different individuals and in the same person with season, state of training, amount of sweat, and possibly with the blood chloride level.[9] It is, therefore, impossible to approximate, without elaborate studies, the salt lost through sweating. It is suggested that during the hot humid days of summer a minimum of 10 Gm. of salt be provided daily either orally or parenterally. If this amount is in excess of that needed the kidney will excrete it. The abnormal losses of water and electrolytes through fistulas, Wangensteen drainage, bile drainage, vomiting, and diarrhea are readily balanced by the parenteral replacement with an equal volume of normal saline or Ringer's solution.[19]

The problem of correcting the dehydration and electrolyte imbalance that is frequently present when the patient first consults a physician is not as simple as is the prevention of dehydration and electrolyte imbalance during hospitalization. Simple dehydration (water deprivation

without electrolyte loss) such as occurs with obstruction of the esophagus and is manifested by thirst, dry mucous membranes, and oliguria is very easily correctable with glucose solution. Salt solution, if given, will not allay the thirst. The situation and consequences are somewhat analogous to the thirsty shipwrecked mariner given sea water to drink. The allaying of thirst and the raising of the twenty-four-hour urine volume above 1,000 c.c. serve as indications that enough glucose solution has been given to a person suffering simple dehydration.

The patient suffering from electrolyte deficiency (diarrhea, fistulas, Addison's disease, profuse sweating), since he is usually able to satisfy his thirst if water is available, experiences neither salt hunger nor thirst even though his extracellular fluid volume (blood volume included) be so reduced that he lies in deep shock.[11, 23, 35] Blood examination shows a high hematocrit, and a high serum protein concentration provided that a normal red blood cell and protein content were present before the electrolyte loss. Chloride and sodium are decreased in the plasma. If the loss of chloride exceeds the loss of base (vomiting, exclusive of achlorhydria) the blood chloride level is more rapidly diminished than is the base.[11] If base loss should balance the chloride loss (vomiting with achlorhydria), or exceed it (biliary or pancreatic fistula), the blood chloride level falls relatively more slowly. In any case, since extracellular fluid volume as influenced by its ionic constituents changes mainly with alterations in its total base content,[28] it is obvious that the blood chloride level is not sufficient to evaluate the severity or the cause of the dehydration in the various gastrointestinal pathologic states. However, as Peters and Van Slyke[29] have stated, the determination of the HCO_3 of the blood together with the determination of chloride would provide a basis for estimating the concentration of base and, as a consequence, a more objective determination of the severity of the dehydration. It is presumed that herein lies the explanation for the occasional difficulty that we have experienced with electrolyte and water replacement when it is universally attempted upon the basis of blood chloride level alone.[30]

Neither do the hematocrit or the serum protein levels serve as an adequate measure of extracellular fluid volume replacement as they are too variable, especially in the pathologic states with which electrolyte imbalance occurs. Consequently, in cases characterized by a primary electrolyte deficiency that show the signs and suffer the symptoms of shock, as a consequence of the decreased blood volume, the alleviation of symptoms and disappearance of the signs of shock, and the maintenance of a satisfactory urine volume constitute an adequate basis for judging the adequacy of the electrolyte and water replacement without recourse to laboratory determination of blood chloride and bicarbonate levels. However, it is hoped that work now in progress in many laboratories may soon enable us to employ more scientific means in the control of electrolyte replacement therapy.

Simple water deficiency and simple electrolyte deficiency although seen as separate entities are very commonly combined.[23] It is obvious from the preceding discussion that a fairly objective clinical approach to the correction of both conditions when in combination may be provided without recourse to laboratory determinations. This is of importance to the general practitioner who does not have ready access to a clinical laboratory and it will become more important in the larger clinics as the labor and monetary shortage imposed by war become more acute.

Since thirst indicates the lack of water in both extracellular and cellular compartments (simple dehydration), its alleviation first with glucose solution (5 to 10 per cent)[38] will correct the simple dehydration. Subsequently, normal saline or Ringer's solution, to which glucose may be added, should be continued at the rate of 200 to 300 c.c. per hour until the signs and symptoms of shock are alleviated. That is, the blood pressure rise and the pulse rate fall reach a plateau, the extremities become warm, the superficial veins fill at approximately the normal rate when occluded, and weakness and apathy diminish in intensity. It is obvious that should the serum proteins be low, complete restoration of blood volume to normal with saline solution should not be expected. In practice, therefore, after 3,000 to 4,000 c.c. of saline solution have been given, hemoglobin and red cell determinations should be made. Should the hemoglobin be below 70 or the red blood cell count be below 3,000,000 it is likely that the serum proteins are low, especially if malnutrition is present or blood loss has occurred. In such a case maximum improvement cannot be expected until blood or plasma has been given in addition to the salt solution. After the initial correction of the dehydration and electrolyte imbalance the principles of volume-for-volume replacement plus 5 Gm. of extra salt daily to provide a slight excess, and the maintenance of a urine volume above 1,000 c.c. will generally serve as adequate guides for subsequent management.

It must be realized that the administration of salt in amounts in excess of those actually required is not without danger, especially in sick individuals. The retention of salt and water results ultimately in edema when the amount of excess salt is less than that which results in significant retention in the normal individual.[1, 6, 19, 20, 37] The dangers of edema developing in a sick surgical patient have been well shown. It is, therefore, highly desirable, especially in the very ill patient, to provide water and salt in amounts as near the physiologic needs of the individual as possible if we do not wish to act as a drag on nature in her attempts to heal.

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A MODIFIED WHIPPLE OPERATION FOR CARCINOMA OF THE HEAD OF THE PANCREAS*

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SINCE the demonstration by Whipple, Parsons, and Mullins, in 1935, that ligation of the pancreatic duct could usually be tolerated in the course of partial pancreatectomy for carcinoma of the ampulla of Vater in man, renewed interest has been aroused in radical surgical approaches to the pancreas. This trend was strengthened by Whipple's report, in 1938, of successful extirpation of carcinoma of the head of the pancreas. Prior to 1941, procedures designed for extirpation of such lesions were in general performed in two stages. One such procedure was successfully carried out by Dr. John R. Paine at this clinic. The patient survived for three months after the second stage operation and died elsewhere of unknown cause, an autopsy not being obtained.

With the advent of vitamin K and more adequate use of blood and plasma transfusions, however, the trend is now toward a one-stage operation. In November, 1941, Trimble, Parsons, and Sherman reported a successful one-stage procedure, the technique being essentially the same as that now in use by Whipple. In this procedure, partial gastrectomy with an anterior Polya gastrojejunostomy was performed, the common bile duct being implanted into the jejunum just distal to the gastric stoma.

Upon review of the pertinent literature, several considerations become apparent with regard to the performance of a satisfactory operation. The first of these is the prevention of ascending cholangitis following anastomosis between the biliary and intestinal tracts, a complication of considerable frequency in the best of hands. Trautmann, Robbins, and Stewart showed in experimental studies in dogs that simple side-to-side anastomosis of bowel to gall bladder uniformly is followed by passage of intestinal content into the biliary tract. Wangensteen concluded that even though this occurs, the essential factor in preventing cholangitis and hepatitis is the prevention of obstruction at the stoma. Bachrach and Fogelson confirmed this in the case of choledochojejunostomy.

Various authors have described procedures intended to prevent reverse flow into the biliary tract. Kausch described a Y procedure somewhat similar to the Roux gastrojejunal anastomosis, and others have offered

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modifications, all, however, with short segments separating the biliary anastomosis from the main enteric stream.

A further consideration is the development of the simplest procedure possible, one with a minimum of anastomoses, etc., a factor demanded by the usual poor condition of these patients. Finally, leakage of pancreatic juice into tissues or suture lines must be prevented. (Verne C. Hunt has reported successful implantation of the pancreas into the end of the jejunum, and T. G. Orr has also had two successful cases.)

I have operated upon a case by a variant of these procedures which seems to overcome the difficulties outlined above. A wide stoma is assured by end-to-end cholecystojejunostomy; regurgitation into the biliary tract is minimized by use of a long jejunal segment separating the biliary from the gastric anastomosis. There are but two anastomoses, and pancreatic digestion is rendered unlikely by adequate use of drainage.

CASE REPORT

History.—H. V. J. (U. H. No. 715130), a man of 64, was admitted on the medical service Dec. 18, 1941, with a one-year history of vague digestive distress and a two-month history of gradually increasing painless jaundice with dark urine and acholic stools. He had lost twenty pounds in the preceding three months and over fifty pounds in the preceding two years. The remainder of the history was irrelevant, except for a story of dyspnea on exertion.

Examination revealed nothing outside normal limits except for jaundice and emaciation. The laboratory work showed hemoglobin 12 Gm. per 100 c.c. of blood. Serum bilirubin was 14.1 mg. per cent. The urine was normal except for bile pigments. Pulse was 60; blood pressure, 109/65; height, 74 inches; weight, 157 pounds clothed. Quantitative examination of the stool for urobilinogen showed passage of 0.7 mg. daily, indicative of complete biliary obstruction and, therefore, carcinomatous obstruction (Watson).

He was given a high vitamin, high protein diet including parenteral vitamin K preoperatively.

Operation.—On Jan. 2, 1942, with a weight of 139 pounds, the patient was transferred to the surgical service and taken to the operating room. The operation was started under cyclopropane, but the anesthetic was changed to ether and oxygen shortly because of the development of auricular fibrillation. Through a long transverse incision, one-third of the way from the umbilicus to the xyphoid, the abdomen was opened. A vertical extension was made upward in the right rectus muscle later in the procedure.

A small discrete tumor was found in the region of the head of the pancreas. It was placed rather high (cephalad) in the head of the pancreas. There was no evidence of spread of the tumor within the peritoneal cavity except for three small irregularities on the surface of the liver. Inasmuch as these irregularities could not be definitely considered to be carcinoma, and in any case did not seem to justify abandonment of all operative procedure, it was decided that radical one-stage resection of the head of the pancreas and duodenum should be performed. The lower end of the stomach was dissected free, and the pylorus was cut between clamps. The lateral avascular ligament of the duodenum was cut down as far as the mesocolon and the duodenum with the tumor attached to the internal margin was rotated forward. Dissection was carried down to the uncinate portion of the head of the pancreas, which was dissected free from the third portion of the duodenum. The

superior mesenteric artery and vein were identified and followed upward, and were found to pass very close to the left lateral margin of the tumor. Nevertheless, it was possible to cut across the head of the pancreas, sparing these vessels. The main duct was tied with silk of five-pound test. The common bile duct was tied with heavy silk and divided near the duodenum. The posterior capsule of the pancreas was sutured to the anterior with mattress sutures of five-pound test silk. At this point it became apparent that the circulation to the last part of the duodenum

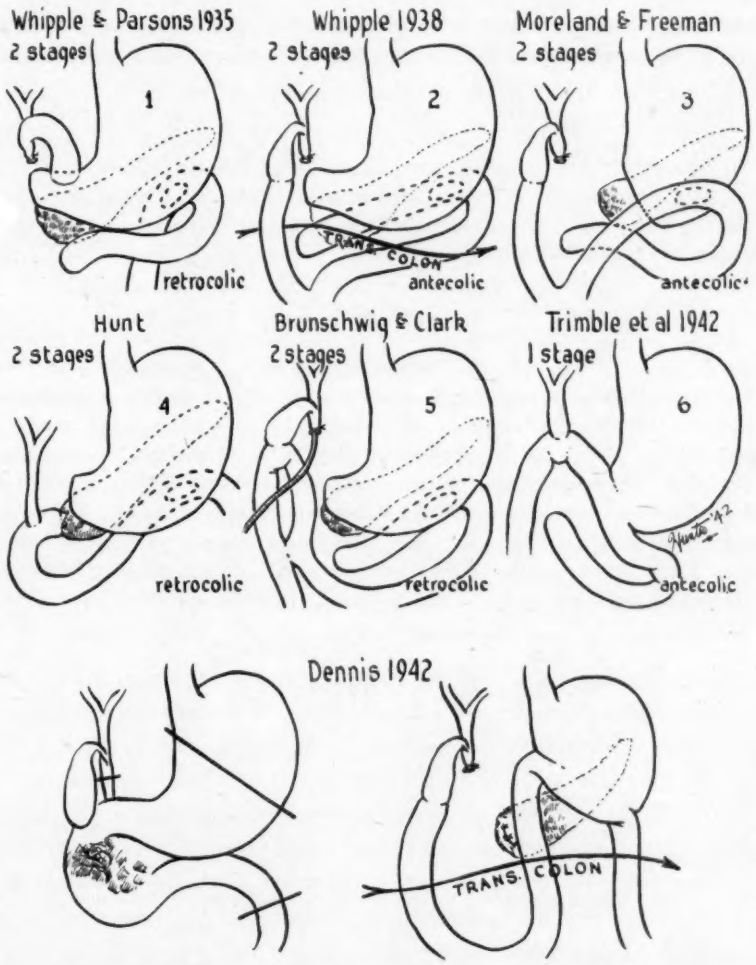

Fig. 1.—Outline diagrams of several operative procedures which have been employed for extirpation of carcinoma of either the ampulla of Vater or of the head of the pancreas.

and to the lowest third of the stomach was inadequate, and both were, therefore, resected, the lines of section crossing the stomach in the midportion, and the jejunum about eight inches below the ligament of Treitz. The gall bladder, which had been found tensely distended, was emptied without spillage by trocar, the remaining end of the jejunum was brought retrocolically through the channel formerly occupied by the duodenum, and an end-to-end cholecystojejunostomy was performed by a closed technique similar to that of Martzloff and Burget, with fine catgut internally and silk mattress sutures externally, a few grains of sulfathiazole being placed between the rows of sutures. Leaving a long (40 cm.) proximal loop, and implanting

a few grains of sulfathiazole between rows of sutures, a retrocolic Polya gastrojejunostomy was performed much as described by Wangensteen. It had been planned to do a Coffey type of anastomosis between the tail of the pancreas and the jejunum below the gastrojejunostomy, but the patient's condition was not satisfactory, inasmuch as he had been having fibrillations for some time and the blood pressure had fallen below 100 mm. Hg. A cigarette drain was brought down to the cut end of the pancreas after all large vessels in the neighborhood and also the ligated end of the common duct had been covered with omentum. The end of the rubber drain was sutured anteriorly and posteriorly to the cut end of the pancreas in such a fashion that any leakage from it would have to escape through the drain, and a tunnel of omentum was made with catgut sutures to surround the drain to a stab wound placed about 6 cm. below the midportion of the incision, a precaution to prevent drainage from reaching the line of closure. Approximately one gram of sulfathiazole was placed in the region of the cut surface of the pancreas. The incision was closed with interrupted five-pound test silk, with implantation of a few more grains of sulfathiazole. The patient received 1,500 c.c. of blood and 400 c.c. of plasma during the seven-hour procedure, and left the operating room in fair condition.

Postoperative Course.—Postoperatively the patient went into acidosis, and the blood sugar rose to 230 mg. per cent, a result attributed to manipulation of the pancreas. The daily administered 20 per cent dextrose solution (1,000 c.c. daily) was, therefore, accompanied by 60 units of insulin per liter the first two days, following which the insulin requirement rapidly disappeared. Immediately postoperatively the patient was digitalized rapidly, but continued to have auricular fibrillation for several days. On the third day bile stained fluid drained through the cigarette drain, and this persisted for thirteen days, the daily volume diminishing gradually from an original 200 c.c., and the bile content also decreasing. A small stitch abscess occurred at fourteen days, but healing occurred quickly on drainage. The cigarette drain was removed at fourteen days. A trial on pancreatic juice obtained from a canine pancreatic fistula prior to dismissal resulted in nausea. He was therefore placed on pancreatin* and polyvitamin capsules on dismissal twenty-one days after operation.

Following dismissal the patient gained ten pounds in eight weeks, and improved in general health and strength. On March 28, he had begun to lose weight and was observed to have bulky, fatty, foamy, strong smelling stools. He also complained of nausea on ingestion of sweet foods. For these reasons he was readmitted for study. A gastrointestinal roentgen study showed rapid emptying of the gastric pouch with no regurgitation of the contrast medium into the proximal jejunal loop. There has been no evidence of cholangitis and no overt evidence of recurrence at the present writing, three and one-half months postoperatively. Preliminary studies indicate absorption of only 65 per cent of ingested fat; further studies are being performed. The patient has ceased losing weight at 129 pounds, following institution of a special diet.†

CONCLUSION

An operative procedure for carcinoma of the head of the pancreas has proved successful in one case. It encompasses excision, also, of

*Eli Lilly and Company.

†After this paper had been submitted for publication, this patient returned with recurrence in the line of incision. Roentgen therapy has been employed, but he is losing ground rapidly at this time (June 24).

the lower half of the stomach and of the entire duodenum. To prevent subsequent cholangitis, internal biliary drainage with a *wide stoma* is accomplished by end-to-end cholecystojejunostomy, and regurgitation into the biliary system is rendered minimal or absent (as shown by roentgen study) by the use of a *long loop* between this anastomosis and the posterior Polya gastroenterostomy.

Pancreatic steatorrhea has followed exclusion of pancreatic secretion from the intestinal tract. Because of this occurrence in this case and in some cases reported elsewhere, consideration of reimplantion of the pancreatic duct into the bowel in such cases is being entertained both here and elsewhere.

ADDENDUM

After this paper had been prepared, an additional case of carcinoma of the head of the pancreas in a man of 67 has been subjected to resection of the lesion. Difficulties were encountered because of very low choledochocystic junction, which was involved in the lesion, and because of arterial anomalies consisting of absence of the celiac axis and origin of the hepatic artery from the superior mesenteric artery, the anomalous hepatic artery traversing the head of the pancreas. Considerable blood loss occurred following removal of the lesion, and large transfusions were necessary before satisfactory repair had been accomplished to the anomalous hepatic artery, the portal vein, the splenic vein, and an anomalous vessel springing from the left gastric to the left lobe of the liver. The procedure was completed with choledocho-enterostomy to the closed end of the jejunum brought through the mesocolon and Polya gastroenterostomy after hemigastrectomy. The patient, however, died shortly postoperatively. Autopsy showed a clean, dry operative field and massive pulmonary edema. Further arterial anomalies were also present.

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PROBLEMS WITH DUODENAL STUMP IN GASTRIC RESECTIONS

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PARTIAL gastric resection has come to be employed frequently in the treatment of benign and malignant lesions of the stomach and duodenum. After it was shown that gastroenterostomy was followed by a considerable number of stomal and jejunal ulcers, many surgeons abandoned this procedure and turned to partial gastric resection as the operation of choice.

The operation of resection is a much more formidable procedure than gastroenterostomy and the technical difficulties are so many that a well-established routine must be developed before a surgeon can expect to escape many of the hazards of this operation.

Most of the articles which have been published on the subject of gastric resection have directed attention to the varied techniques used in establishing the anastomosis between the cut end of the stomach and jejunum. The importance of proper closure of the duodenal stump in the Polya-Reichel or Hofmeister-Finsterer type of Billroth II partial gastrectomy is undoubtedly appreciated by surgeons. Clute[1] has stated that no part of a gastric resection is more likely to be followed by fatal complications if improperly done than the closure of the duodenal stump. Yet critical evaluations of this problem and significant contributions toward improving and strengthening the closure have been sparse.

In this paper we propose to discuss certain methods and techniques which we have found helpful in the prevention of postoperative complications arising from the closed blind-ended duodenal stump.

Complications.—Following gastric resection, *hemorrhage* may occur which not uncommonly destroys the life of the patient. This may take place within the duodenal lumen from an unresected ulcer, or into the peritoneal cavity from injury to the gastroduodenal artery or its branches. Another complication may be the development of an *abscess* due to leakage from the closed duodenal stump. Still another possibility is that of *frank disruption* of the closed stump. In the case of abscess formation or disruption of the sutured duodenum, there not infrequently follows a *duodenal fistula* which permits the duodenal contents to pour out over the skin of the upper abdomen. The latter complication has a very high mortality rate.

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These complications may be due to a combination of various factors in any one case, but in order to present the subject more clearly and to emphasize the importance of each factor, the problem will be discussed under two main headings: 1. The location of the ulcer; 2. The intraluminal pressure in the duodenal stump.

LOCATION OF THE ULCER

Portis and Jaffe,[5] in a recent study of peptic ulcer based on necropsy records, found that 62 per cent of 158 duodenal ulcers were located on the posterior wall of the duodenum, while 38 per cent were on the anterior wall. When the ulcer is on the anterior wall of the duodenum, close to the pyloric vein, closure of the stump presents comparatively few difficulties. Such ulcers are also the least likely to have had hemorrhages of great severity. When the ulcer is located on the posterior wall of the duodenum, however, there is much greater likelihood of its having been complicated by massive hemorrhage or by pyloric stenosis.

These complications, hemorrhage and stenosis, often make operation necessary. The extreme importance of adequate preparation for surgery, which, in the case of hemorrhage, should include multiple transfusions, cannot be stressed too much. However, the technical details of surgical management in such cases are of equal importance. If the operation is done for hemorrhage, one frequently finds that a large branch of the gastroduodenal artery has been eroded and lies in the depths of the penetrating ulcer, surrounded by pancreatic tissue. The ulcer is often near the duodenohepatic ligament and not infrequently this region is infiltrated and edematous. To isolate and ligate the gastroduodenal artery above the convexity of the duodenum has been suggested as a means of controlling hemorrhage from the eroded vessel in the ulcer depth. It is necessary, however, to ligate the artery below the duodenum where it branches into the pancreatic and epiploic divisions. The collaterals in this area are so numerous that it is a great problem to isolate and ligate accurately all of the major branches which might contribute to severe bleeding due to erosions involving the gastroduodenal artery as it passes behind the first portion of the duodenum. If the operation is done for pyloric stenosis, the obstruction of the gastric outlet may be found to be due to the edema and inflammatory infiltration resulting from the ulcer's penetration of the head of the pancreas (Fig. 1, *B*). In either of these cases, if one were to attempt to free up this duodenum from the pancreas and carry the dissection beyond the ulcer, considerable difficulty would be encountered in establishing a line of cleavage and in maintaining the continuity of the duodenal wall. The tissues are inclined to be thickened and friable and the bleeding following dissection is often profuse. The proximity of the main trunk of the gastroduodenal artery adds to one's difficulties (Fig. 1, *A*). Even if one were successful in freeing up the duodenum, there still would remain the problem of mobilizing enough wall for an inversion which would be adequate to prevent leakage or actual disruption.

The presence of the common duct in this region presents an additional hazard. In pursuing the attempt to close adequately the duodenal stump, several cases have occurred in which the common duct has been completely obstructed (Fig. 1, *C*). This is a most unfortunate accident, as it necessitates extensive surgery and reconstruction for its relief. The fact that a mild transient jaundice, due to angulation or temporary

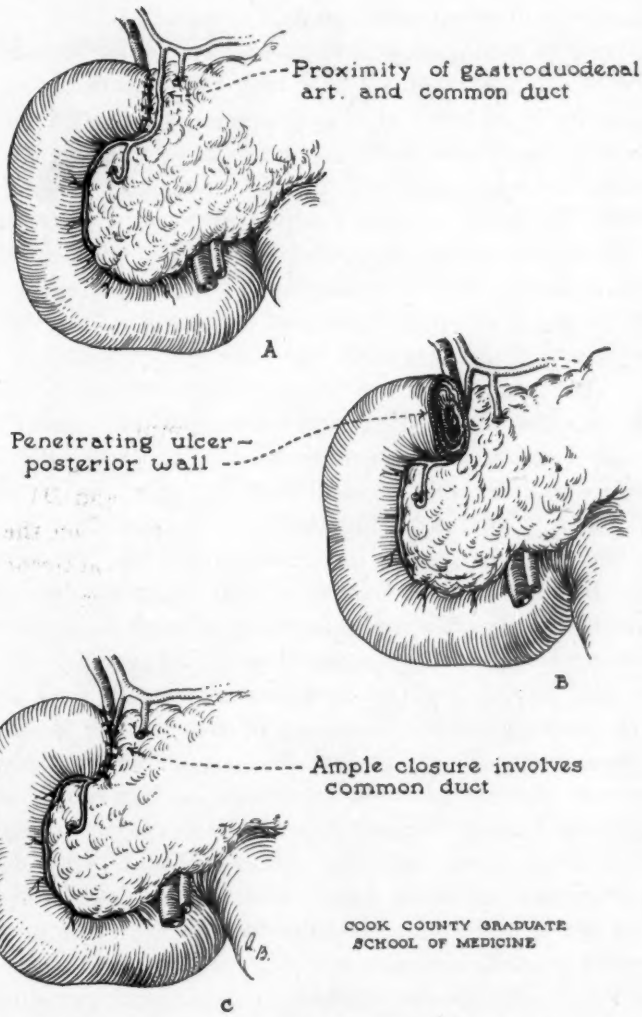

Fig. 1.—Problems and accidents common in closure of the duodenal stump.

compression of the common duct, not infrequently appears following a gastric resection and rights itself after a few days, is undoubtedly responsible for unwarranted delay in these cases where the common duct is completely obstructed by its involvement in the duodenal closure. In the hope that each case of postoperative icterus may be of the temporary type, further surgery is not attempted until the condition has shown no tendency to improve spontaneously and the patient is deeply jaundiced.

From this brief discussion it becomes obvious that the vulnerable posterior wall of the duodenum is one of the principal hazards in gastric resection.

The necessity for resecting the ulcer area in such cases does not seem to be great, as there is a marked tendency for these ulcers to heal as soon as gastric secretion is completely diverted. Ginzburg and Mage,[4] in a recent study, found that 56 of 58 duodenal ulcers from which the gastric secretion had been diverted had healed.

In these cases of posterior wall ulcer we have found a great advantage in a method of closure which we have termed "closure of the duodenum with tamponade." In brief, it is developed along the following lines.

The duodenum is divided between clamps at or near the pyloric orifice. The proximal duodenum is freed up very cautiously and no attempt is made to resect the ulcer area on the posterior wall. After preliminary closure of the stump with a Kerr-Parker stitch or simple over-and-over suture (Fig. 2, *A* and *B*), the duodenum is then plicated longitudinally for a distance of one to one and one-half inches (Fig. 2, *C* and *D*). This practically always extends beyond the ulcer crater, which is on the posterior wall. The purpose of the plication is to crowd the anterior free wall down into the penetrating ulcer crater on the posterior wall, as shown in the diagrammatic cross-section of Fig. 2, *D*. In many ways this procedure follows the principles of the obliterative aneurysmorrhaphy of Matas. The enfolding not only tamponades the ulcer from which the hemorrhage, if any, has come, but it also protects the weak stump from leakage and disruption. This is explainable on the basis that the transverse plication and narrowing give an added reinforcement and take the pressure from the inverted duodenal stump.

Fogelson and his co-workers[3] have undertaken to work out on dogs an accurate quantitative measurement of the various methods of duodenal stump closure. They felt that the best method for measuring the strength of the closure would be to determine how much air pressure was necessary to blow out the stump. This was done by sectioning the duodenum of a dog at its distal untraumatized end (after a Polya type of gastric resection had been done), inserting a glass tube, which was then tied in place, and connecting the tube to a bicycle pump through a specially constructed large size mercury manometer. The intraluminal pressure of the duodenum could thus be increased until rupture occurred, at which moment the pressure reading on the manometer was noted. The five different methods of closure employed were as follows:

1. Von Haberer open method without clamps or crushing.
2. Crushing clamp method of Kerr-Parker.
3. Simple ligature followed by purse string without clamps or crushing.
4. Same as method 3, using silk instead of catgut.
5. Duodenal tamponade in addition to Kerr-Parker clamp method.

In the last method, in every instance, the duodenum ruptured first at the site of the transverse stitches under pressures higher than those to which the human duodenal stump would ever be subjected (222 mm. of mercury), thus demonstrating the added protection which the transverse plication gives to the duodenal stump.

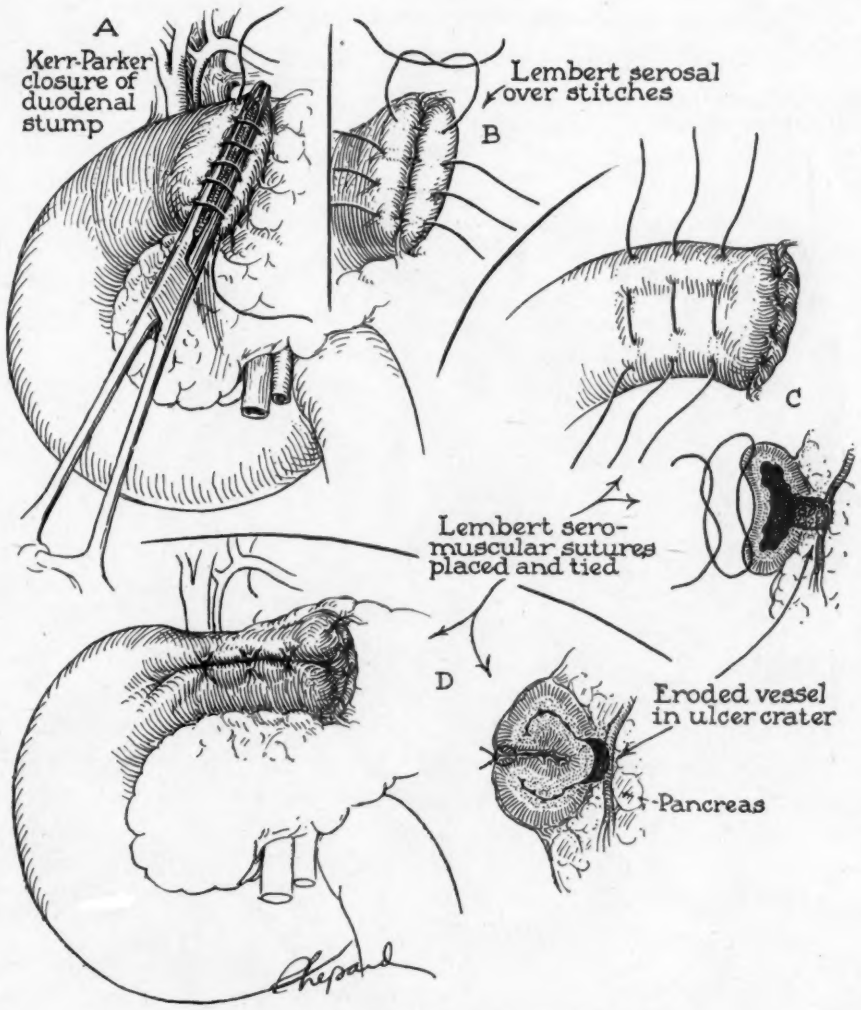

Fig. 2.—Steps in duodenal tamponade.

INTRALUMINAL PRESSURE IN THE DUODENAL STUMP

When gastric secretion has been diverted, there still remains the flow of the bile and pancreatic juices into the proximal duodenum. This is also augmented by the secretions of the mucosa itself. The total amount of these secretions may vary within wide limits, but generally can be said to be in the neighborhood of 1,000 to 1,500 c.c. in twenty-four hours. With such an amount of fluid pouring into this short portion of the intestinal tract, one can understand readily that any inter-

ference with the outflow of this secretion would produce within a short time a considerable accumulation and pressure within this segment. Wangensteen[7] has reported that in an obstructed duodenum in a dog, the intraluminal pressure varies between 20 and 45 cm. of water pressure. In 1929, Dragstedt[2] called attention to the fact that the duodenum was more rapidly and severely susceptible to the effects of distention than any other portion of the intestine.

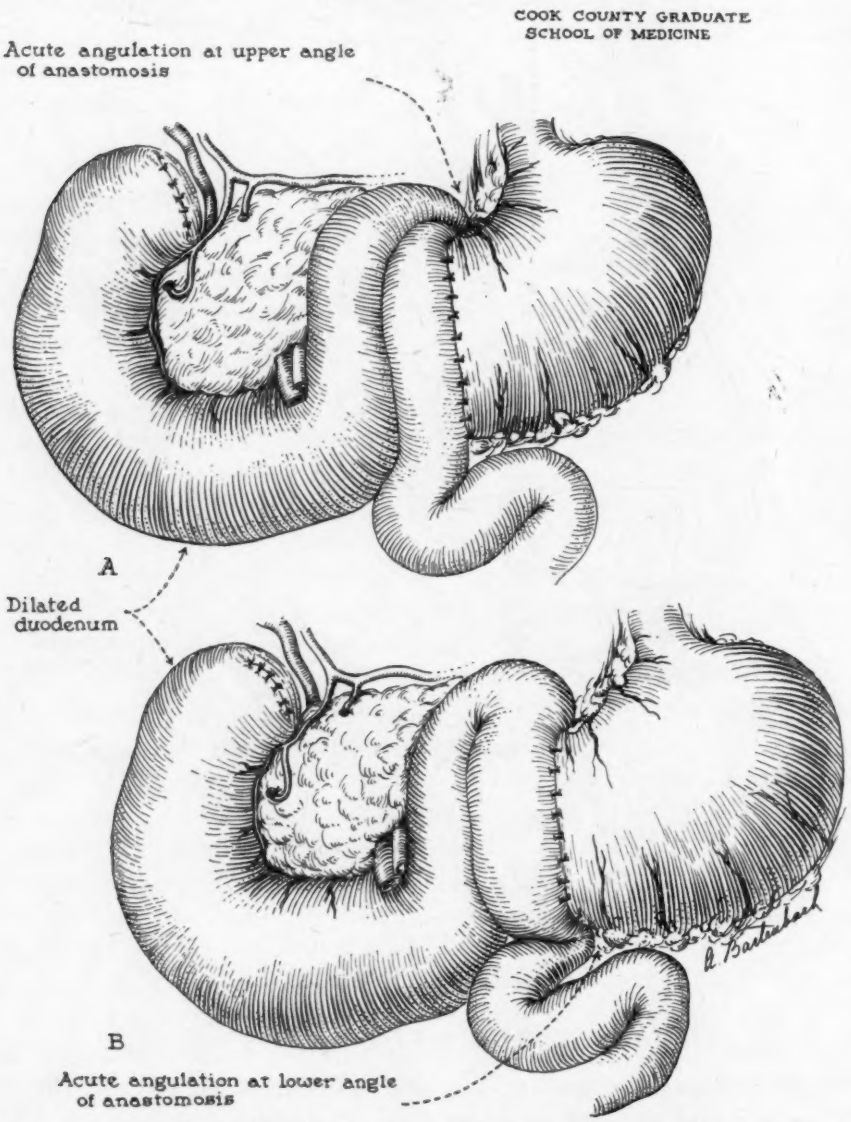

Fig. 3.—Errors in anastomosis which lead to closed loop obstruction of the duodenum.

Let us, therefore, direct our attention toward this mechanical obstruction to the outflow of the duodenal contents.

When an anastomosis is made between the cut end of the stomach and the antimesenteric border of the jejunum, rather sharp angulations

are bound to be created where the jejunum is fixed to the greater curvature and the lesser curvature of the stomach. Certain errors in handling the anastomosis may accentuate this angulation, which may result in partial or complete obstruction of the jejunal lumen. This in turn may create a closed loop obstruction of the duodenum. This was well pointed out by Raffel[6] recently when he said, "The cause of disruption of the duodenal suture line is believed by some surgeons to be obstruction (early) at or near the stoma of the anastomosis, and large quantities of duodenal contents are found in the peritoneal cavity when this complication occurs."

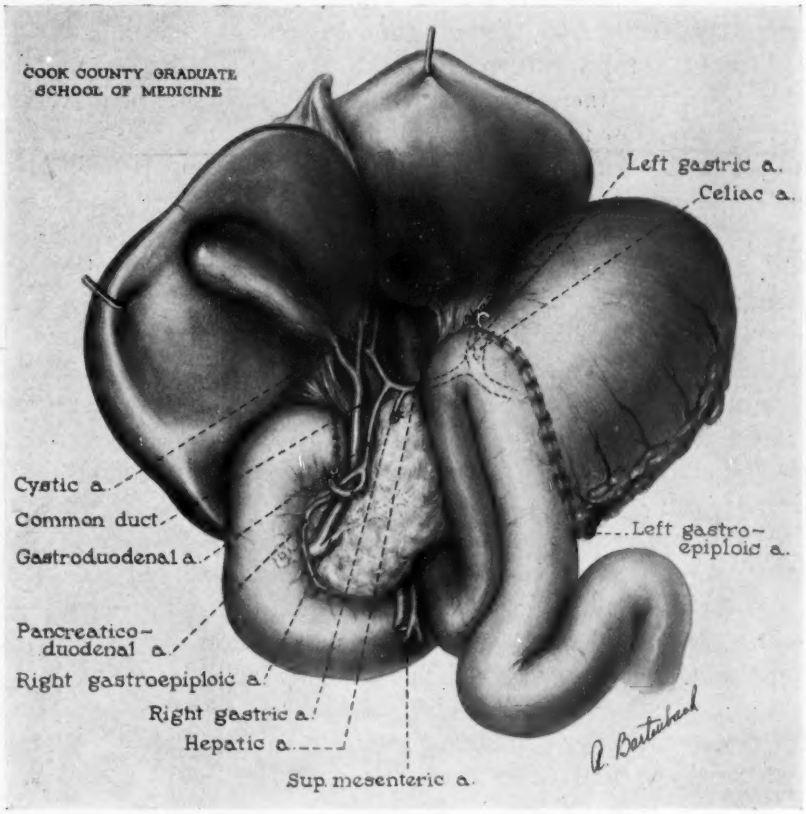

Fig. 4.—Properly managed anastomosis.

Errors in handling the anastomosis may be rather arbitrarily divided into three groups: (1) In some instances, the obstruction may result from the manner in which the stomach and anastomosed jejunum are delivered through the transverse mesocolon, (2) obstruction may be due to an improper suturing of the transverse mesocolon to the stomach proximal to the gastrojejunal anastomosis line, (3) jejunal angulations may result from the improper suturing at the lesser and greater curvature angles of the anastomosis.

Fig. 3, *A* illustrates an angulation produced at the lesser curvature. The use of the technique suggested by Finsterer for protecting this site, that is, the suturing of the proximal loop of the jejunum to the lesser curvature of the stomach for a distance of 1 to 2 cm. above the corner of the anastomosis, may account for some of the obstruction in this region. If his method is correctly used, no angulation will occur, but if the corner is sutured too high along the lesser curvature, angulation is very likely to result. This will cause obstruction to the outlet of duodenal contents, and greatly increase the intraduodenal pressure.

In illustration *B* of Fig. 3, an angulation is shown at the greater curvature. This may be produced by carrying the jejunum around the greater curvature angle in order to make it seem more secure, or it not infrequently results from torsion of the anastomosed jejunum during the procedure of serosal suturing. When the angulation occurs at the greater curvature, there would seem to be even more risk of frank disruption of the closed duodenal stump. This is due to the fact that the secretions and regurgitated contents of the stomach are added to the secretions which arise in the duodenum and are brought there through the ampulla. The forceful contractions of the remaining fundic portion of the stomach may increase greatly the pressure within the proximal duodenum.

If the angles of the anastomosis are kept in proper alignment, these unfortunate conditions should not develop, that is, by placing the beginning sutures of the anastomosis exactly through the antimesenteric border of the jejunum and the greater curvature, and by finishing the anastomosis exactly at the antimesenteric border of the jejunum and the lesser curvature. Fig. 4 shows a completed anastomosis wherein the angles of the anastomosis are properly managed.

Raffel has suggested a method for decompressing not only the stomach, but also the duodenal loop, which in addition makes it possible to feed back into the normal distal jejunal loop the secretions collected from the stomach and duodenum, plus such exogenous material as might be required. The rationale and wisdom of such a procedure seem obvious, and it might well offer a further protection against leakage and disruption of the closed duodenal stump.

SUMMARY

While the importance of adequate duodenal stump closure in gastric resection is recognized by most surgeons, critical evaluations and contributions to strengthening and improving the closure have been sparse.

When resection is done for an ulcer on the vulnerable posterior wall of the duodenum, the difficulties of closure of the duodenal stump are greatly increased. In the case of hemorrhaging peptic ulcer, failure can be attributed frequently to the technical steps which do not efficiently prevent recurrence of hemorrhage. In many instances the bleeding is from an open eroded vessel which cannot be successfully approached, as

it lies in the ulcer bed surrounded by pancreatic tissue. In these cases and in cases of pyloric stenosis due to edema and inflammatory infiltration resulting from the ulcer's penetration of the head of the pancreas, it is often extremely difficult to free up the duodenum from the pancreas and carry dissection beyond the ulcer. Even if one were successful in freeing up the duodenum, there would still remain the problem of mobilizing enough wall for an inversion which would be adequate to prevent leakage or actual disruption. There is also the dangerous possibility of involving the common duct in an adequate closure of the duodenum.

It is my feeling that too much emphasis has been placed on the necessity of resecting the ulcer itself, particularly in cases of penetrating posterior wall duodenal ulcers. Even the most chronic of these tend to heal when gastric secretion has been diverted.

A method of duodenal closure has been presented, which I have found particularly helpful, both in lessening the number of hemorrhages, and in protecting the weak stump against the back pressure which under ordinary circumstances might encourage it to blow out. Hemorrhage is prevented by crowding the anterior wall of the duodenum down to act as a plug to the ulcer bed on the posterior wall. Pressure on the duodenal stump is alleviated by the transverse plication and narrowing of the duodenal lumen just proximal to the stump.

The various technical errors which lead to marked increase of intraluminal pressure of the duodenum can be avoided by scrupulous attention to the mechanics of the gastrointestinal anastomosis.

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BENIGN TUMORS OF THE STOMACH*

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THE purpose of this paper is to review nine cases of benign tumors of the stomach gathered from the records of the New York Hospital since its opening in September, 1932, through December, 1940. Three of the nine cases had already become malignant at the time of operation, leaving a total of six tumors in the above period which could be classified strictly as benign. Abstracts of the histories and findings in these cases will be noted at the end of the paper.

In the group of nine cases described, the average age was 44 years; the youngest patient was 24 years of age, and the oldest, 58. The incidence of sex is unusual, in that of the entire group of nine cases only one patient was a male.

Benign tumors of the stomach are not common. When one considers the number of roentgenologic examinations of the stomach that are made each year at the New York Hospital, the incidence of benign tumor is very small, for in the x-ray department an average of about twenty examinations of the stomach are made each day. The number of working days in a calendar year at the hospital is about 270. This means that, in round numbers, 5,400 roentgenologic examinations are made of the stomach yearly, and for the period included in this report (eight years) the number of examinations approximate 43,200. During this time only six benign tumors of the stomach were found. The ratio, then, of the number of benign tumors to the number of roentgenologic examinations of the stomach at New York Hospital is about 1 to 7,200.

In the past the ratio of malignant to benign tumors of the stomach was given as about 200 to 1. At the New York Hospital within the period noted above, there were 289 patients with carcinoma of the stomach admitted to the pavilions. The life histories of these patients are being studied carefully by Dr. William A. Cooper. One hundred and five more cases of carcinoma of the stomach were seen on the private and semi-private services. Three hundred and ninety-four cases, then, of carcinoma of the stomach were seen during this period of time in which we collected the data on six benign tumors. The ratio of malignant to benign tumors, therefore, was much less than 200 to 1 and was in fact about 66 to 1.

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Numerous examples of benign gastric tumors have been described accurately in the literature since one of the earliest cases was reported by Gibson before the New York Surgical Society in 1907. With an increased appreciation of the clinical findings in these cases and with the refinements of modern roentgenologic technique, there should be little difficulty in making the diagnosis of benign gastric polyp. My own experience with these cases, however, has convinced me that examples of these benign tumors are constantly being overlooked. The importance of recognizing them early lies in the fact that such tumors are frequently the cause of serious complications. To quote Conway: "The fact that a new growth of the stomach may be benign assumes a practical aspect in view of the importance of conserving such an organ as the stomach." Early diagnosis, followed by immediate operation, obviously will avoid these complications.

Malignant degeneration is the gravest complication which may occur in these tumors. In fifty-eight cases of benign gastric tumors (which included all types of tumors, such as the fibromas, lipomas, and adenomas) reported by Balfour and Henderson in 1927, malignant degeneration was found in only two or 3.5 per cent. The percentage of malignant degeneration is not found to be so low in other series of cases, nor in those cases in which the condition has existed unrecognized for a comparatively long period of time. As a matter of fact, adenomatous polyps and leiomyoma are especially prone to undergo malignant degeneration. McRoberts, reporting from the Mayo Clinic in 1933, presented five cases of adenoma of the stomach which he personally had observed during the preceding year and one-half. In four cases, or 80 per cent, meticulous study of serial sections revealed unquestionable evidence of malignant change. In a series of adenomatous polypi carefully studied by Eliason and Wright, carcinomatous change was found in eight of twenty-three cases, an incidence of 35 per cent. In 1934, Benedict and Allen reported seventeen cases of gastric polypi from the records of the Massachusetts General Hospital, and in this group seven, or 41.2 per cent, showed evidence of malignant degeneration. In a recent publication by Lahey and Colcock, five out of seven of the patients, or 71 per cent, operated upon in the Lahey Clinic for leiomyomatous tumors, showed sarcomatous degeneration. In the New York Hospital series of nine cases, three of them, or 33⅓ per cent, had become malignant.

The next most important complication of these gastric tumors is hemorrhage. Anemia and the presence of occult blood is greater in association with this condition than with ulcer of the stomach. Severe bleeding, with hematemesis and melena, while it may occur, is not characteristic of benign gastric polypi, but moderate bleeding, with gross or occult blood in the stool, is quite common. Anemia is one of the most frequent and characteristic signs of benign tumor of the stomach. The

anemia is usually of the secondary or microcytic type, but in long-standing cases it may progress until it is suggestive of the primary type. Patients with obscure anemias or pernicious anemias should be subjected to roentgenologic examination of the gastrointestinal tract. In this connection it is interesting to note that in seventeen cases reported by Benedict and Allen from the Massachusetts General Hospital, primary anemia was the first diagnosis in five, or an incidence of 30 per cent. In our own series of nine cases, a primary diagnosis of pernicious anemia was made in two cases, but a moderate to severe secondary anemia was present in all the others.

SYMPTOMS AND SIGNS

Benign tumors of the stomach, as a rule, do not cause marked symptoms unless they are complicated by bleeding or intermittent obstruction of the pylorus, or unless because of their size and extent they interfere with gastric motility and secretion. Given a patient with anemia and achylia gastrica, who on x-ray examination reveals the characteristic punched-out smooth defect in the stomach or first portion of the duodenum, the diagnosis of benign tumor of the stomach is certain. Absence of free hydrochloric acid in the gastric contents was a constant finding in our cases. Pyloric obstruction, usually intermittent, occurs in a small percentage of the cases. These are the ball-valve type of tumors which are attached to the posterior wall of the stomach and develop a long mucous membrane pedicle, at first obstructing the pylorus in the manner of a ball-valve and then, finally, prolapsing into the duodenum, where they remain. Our series includes one of these interesting tumors, which was seen by x-ray and diagnosed as a benign tumor of the stomach which had herniated through the pylorus into the duodenum. On roentgenologic examination in this case, the tumor appeared to be entirely within the duodenum and to have its origin there, but exploration disclosed that its pedicle was on the gastric side of the pylorus. There are no characteristic digestive symptoms which produce a syndrome on which the diagnosis of benign tumor could be made.

ROENTGENOLOGIC FINDINGS

With expert radiologic examination of the stomach, a greater number of accurate diagnoses have been made. Benign tumors present certain roentgenologic signs which differentiate them from malignant or inflammatory lesions. However, the differentiation cannot always be made with certainty by means of x-ray. One of the most interesting cases reported in this group was a case of tumor of the stomach which had been diagnosed by x-ray as an inoperable carcinoma. When it was decided to perform a palliative operation on this patient because of persistent vomiting, it was found that she had a benign tumor of the stomach which could be locally resected.

The following roentgenologic findings are characteristic of benign tumors:

1. They produce a filling defect that is circumscribed and punched out in appearance.
2. The filling defect is usually on the gastric walls, leaving the curvature regular and pliant.
3. In inflammatory and malignant lesions, the rugae are obliterated in the immediate area of the tumor, but the rugae surrounding a benign tumor are nearly normal in their arrangement and distribution.
4. They cause little or no disturbance in peristalsis and retention is uncommon, except when the lesion is at or near the pylorus.
5. They do not reveal a niche, nor is there any incisura or other evidence of spasm.
6. They are rarely sufficiently large to be palpated.

If a polypoid tumor prolapses into the duodenum, it will produce a central translucence in the bulbar shadow which is typical. This occurred in one of our cases in which the diagnosis was made before operation. It is true, therefore, that the diagnosis of benign tumor of the stomach is being made more often and more confidently in the present than it has been in the past.

PATHOLOGY

Benign tumors may arise from any of the several coats of the stomach and, according to the tissue of origin, may be divided into epithelial and mesenchymal. Included in the epithelial group are the adenomas, adenopapillomas, adenomyomas and fibroadenomyomas, fibromas, lipomas, and the rare angiomas and osteomas. The leiomyomas, the most common of the benign tumors, constitute about 35 per cent of all benign tumors of the stomach. In a review of the literature by Minnes and Geschickter, who collected 931 cases, 341, or 36.6 per cent, were leiomyomas. In the group of cases reported by Eliason and Wright, 60 per cent were leiomyomas. However, in the nine cases of our series which were operated upon and subjected to histologic examination, there was one leiomyoma and one leiomyosarcoma. Seven tumors were of the type commonly called polyps, that is, epithelial adenomas.

TREATMENT

In the majority of cases of benign tumors of the stomach, local excision, rather than resection, is indicated. The situation of the tumor, of course, determines the best approach. The procedure most frequently used in our series was transgastric excision, performed through an incision in the anterior wall of the stomach, and division of the mucous membrane pedicle. In operating on the large tumors, and in those cases in which the frozen section indicated malignant change, partial gastrectomy was the procedure of choice.

CASE REPORTS

All the surgical pathologic reports in the following cases were made under the supervision of Dr. N. Chandler Foot.

Fig. 1 (Case 1).—Typical punched-out and circumscribed filling defect of benign polyp in duodenal cap.

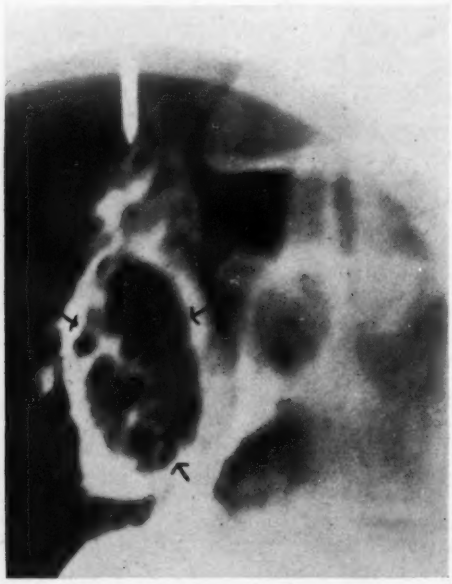

Fig. 2 (Case 1).—Spot film of same tumor shown in Fig. 1.

Case 1 is typical of a benign tumor which had prolapsed through the pylorus and had come to rest in the first portion of the duodenum. I personally observed it and did the operation, diagnosing it as a benign gastric polyp before operation.

CASE 1.—S. W. (New York Hospital No. 173873), female, aged 24 years, was admitted July 1, 1937, with a complaint of indigestion and weakness for the past three years. There was no history of any previous serious illness or operation. In 1935 she had been admitted to another hospital where she was treated for secondary anemia. For the past three years she had been suffering from epigastric distress and a feeling of fullness which came on in paroxysms. There had been no vomiting. In May, 1937, a gastrointestinal series revealed a central filling defect in the duodenal cap, which was not at that time interpreted correctly. A gastric analysis

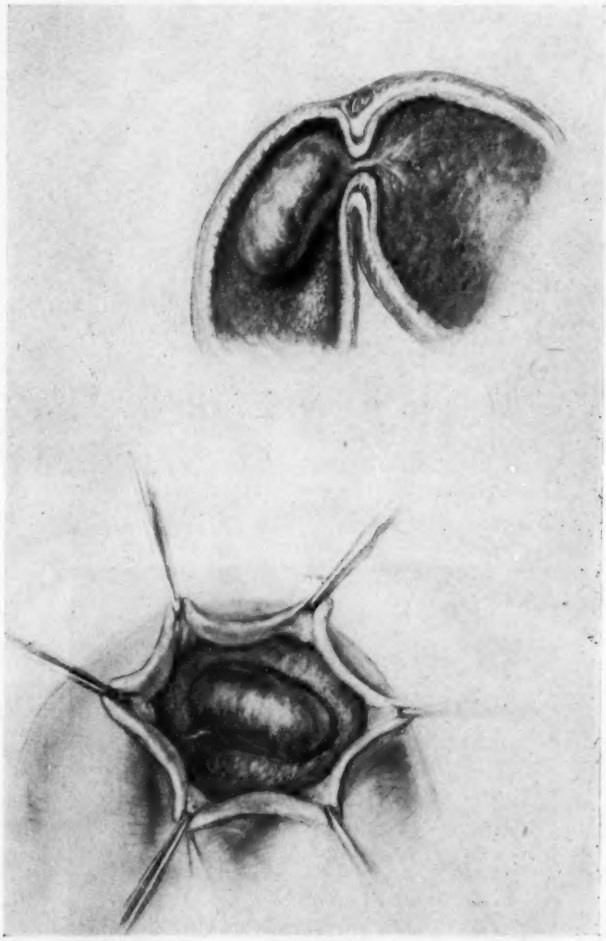

Fig. 3 (Case 1).—Drawing of polyp at operation. At top, note prolapse through pylorus into duodenum with mucous membrane pedicle attached to posterior wall of stomach. At bottom, note small incision through anterior wall of stomach showing polyp and pedicle just before excision.

revealed no free hydrochloric acid at this time. The physical examination was essentially negative. The abdomen was soft and no tumors were palpable. The hemoglobin was 75 per cent and two stool examinations were positive for occult blood. Fluoroscopy and roentgenograms of the gastrointestinal tract revealed a normal

stomach. The duodenal cap showed a displacement of barium measuring 2½ cm. in its longest dimension (Figs. 1 and 2, Case 1). On one of the films there was a suggestive pedicle extending through the pylorus. The impression was that this was a gastric polyp which had prolapsed through the pylorus into the duodenum. At operation a small round, doughy tumor was palpated in the first portion of the duodenum. During palpation the tumor slipped back through the pylorus into the stomach. A short, longitudinal incision was made then on the anterior wall of the

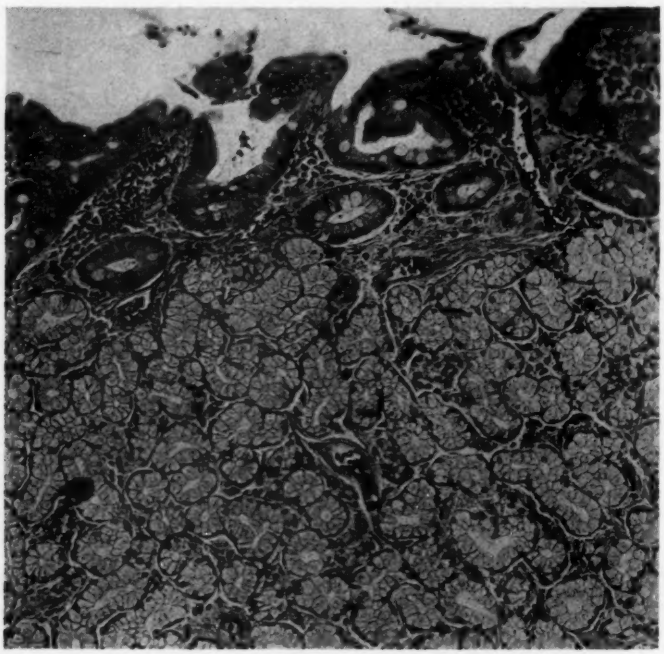

Fig. 4 (Case 1).—Section of polyp showing hypertrophied pyloric glands with a high degree of vascularization and numerous small areas of erosion of the covering epithelium.

Fig. 5 (Case 1).—X-ray six months after operation; normal stomach and duodenum.

stomach, just above the pylorus and midway between the two curvatures. On opening the stomach through this incision, a smooth round polyp with a mucous membrane pedicle was found attached to the posterior wall (Fig. 3, Case 1). This was excised with its pedicle, locally, and the stomach then closed transversely with mattress sutures of fine black silk. The abdomen was closed in layers with interrupted sutures of the same material. Convalescence was uneventful. The patient was discharged on the twelfth day after operation.

Pathologic Report.—The specimen is a polypoid tumor mass 22 by 13 by 7 mm. in size. It is soft and covered with reddened mucosa, which is in the main very smooth. On section it is found to be made up of glandular complexes which are putty colored and often umbilicated with a small red dot at the middle.

Microscopic Examination.—Most of the section is composed of hypertrophic glands which resemble Brunner's glands. Strands of fibrous tissue run between these glands, separating them into nodule-like areas. The covering epithelium shows a high degree of vascularization and numerous small areas of erosion, which probably account for the bleeding in this case (Fig. 4, Case 1).

Diagnosis: Benign polyp of the gastric mucosa.

X-ray examination of the gastrointestinal tract six months after operation showed the stomach to be normal throughout. The polyp is no longer seen either in the antrum or in the duodenal cap and the bulb fills well (Fig. 5, Case 1).

The patient reported three years after operation in good condition and with no symptoms referable to the stomach. The blood picture was normal.

In this second group are three cases of tumor of the stomach which had become malignant at the time of operation.

CASE 2.—P. O. (New York Hospital No. 127343), a woman, aged 43 years, was admitted March 30, 1936. Nine years before admission she began to have some epigastric discomfort with frequent eructations. Three years ago, because of the persistence of these gastric symptoms, her stomach was x-rayed and she was told that she had a tumor of the stomach. Six months before admission her symptoms became worse and were accompanied by daily aching pains in the upper abdomen and back. X-rays again revealed a tumor of the stomach. She had lost about fourteen pounds in weight. On admission, the physical examination was essentially negative, except that palpation of the abdomen suggested a mass in the mid-epigastrium. Laboratory examinations revealed 60 per cent hemoglobin with 3,500,000 red blood cell count. There was no free hydrochloric acid in the gastric contents after histamine, and the stool was positive for occult blood. Fluoroscopy and films of the gastrointestinal tract showed a lobulated lesion on the posterior wall of the pars media. The rest of the stomach and duodenum appeared to be normal (Fig. 6, Case 2). At operation a soft, polypoid, apparently benign tumor, was found, which arose from the anterior wall of the stomach and the pars media. The stomach was opened and the tumor locally excised. Frozen section, however, revealed a carcinomatous polyp. Accordingly, a gastric resection of the Polya type was performed.

Pathology.—The specimen consisted of a piece of tissue measuring 4½ by 3 by 1½ cm. in size, at one end made up of a pale mushroomlike mass 2½ cm. in diameter and raised 1 cm. above the surrounding mucosa. The rest of the tissue was composed of reddened polypoid gastric mucosa. The consistence of the pale mass was very firm without being stony hard. Sections revealed the presence of a tumor of metaplastic glandular tissue. The glandular epithelium was extremely anaplastic in appearance and there were many mitotic figures present. There was deep infiltration of the tumor cells (Fig. 7, Case 2).

On follow-up three years after operation, the patient ate everything without distress and was working. Her color was good and the wound well healed. No

masses were palpated in the abdomen, and the liver was not enlarged. Film and fluoroscopic examination of the gastrointestinal tract showed the stump of the stomach to be small in appearance, which was consistent with the previous operation. It emptied well and the remaining part of the stomach appeared to be normal throughout.

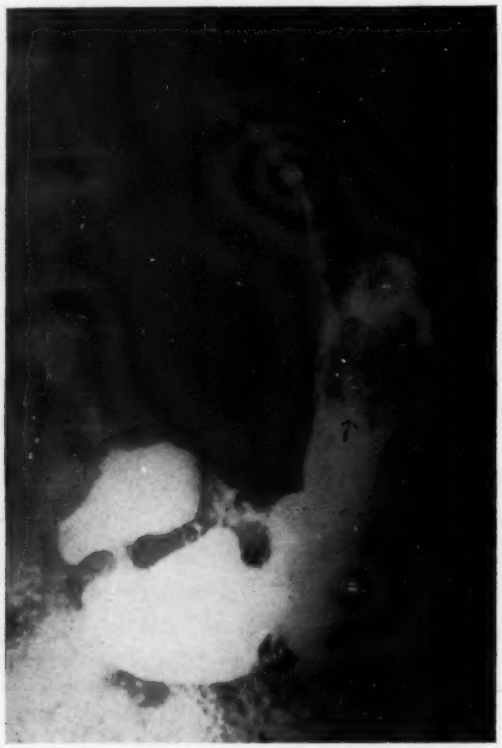

Fig. 6 (Case 2).—X-ray film of stomach showing lobulated lesion in the pars media.

Case 3.—F. E. (New York Hospital No. 71840), a 52-year-old woman, was admitted Aug. 3, 1934, and discharged Sept. 12, 1934. This patient came in with a complaint of epigastric pain and distress. She also had an eleven-year-old story of diarrhea and generalized abdominal cramps due to mucous colitis. For two years previous to her admission, she had been very weak and had lost twenty pounds in weight. Her appetite was poor and there had been frequent spells of vomiting. On physical examination, she appeared to be fairly well nourished. No masses were palpated in the abdomen. Urine was negative, and hemoglobin 85 per cent with a red blood cell count of 3,980,000. In the gastric contents there was no free hydrochloric acid, even after stimulation with histamine. Fluoroscopy and films of the gastrointestinal tract showed an oblique stomach, medium in size and position. The duodenal cap had an unusual appearance. The barium seemed to be displaced by a foreign body. Findings were strongly suggestive of a polyp in the pyloric end of the stomach, probably malignant in character (Fig. 8, Case 3). When the peritoneal cavity was opened at operation, Aug. 17, 1934, about one liter of thin green fluid escaped. Edematous, boggy, indurated areas were found in the greater omentum. There were a number of small white deposits in the liver, 1 to 2 mm. in diameter. The stomach was explored and a mass found in the region of the pylorus. This could be moved from side to side within the lumen. It apparently rose from the posterior wall, or surface, of the prepyloric region and measured about 6 cm. by 2 cm. in size. Two small pin-point white deposits in the mesentery of the ileum

were excised and sent for biopsy. Frozen section was reported as carcinoma. It was decided that a resection of the pylorus or a gastroenterostomy was not justifiable. The diagnosis then was malignant polyp of the prepyloric region with multiple hepatic and peritoneal metastases.

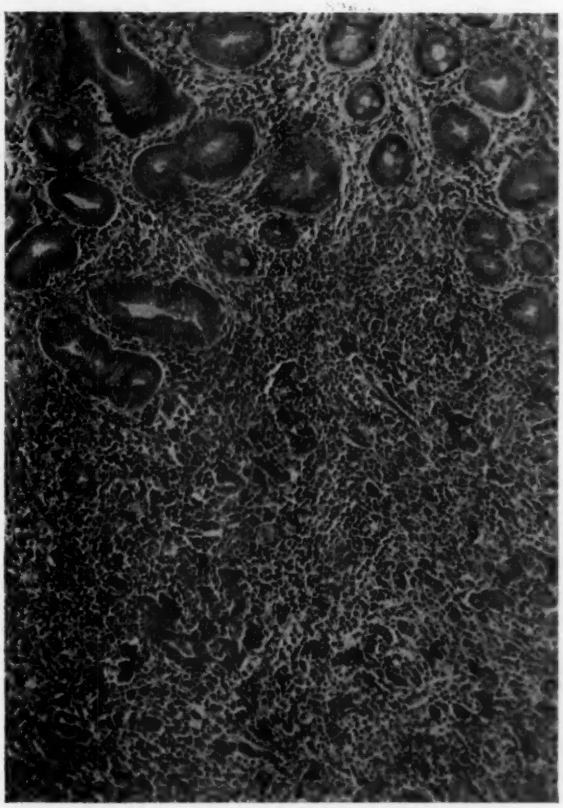

Fig. 7 (Case 2).—Photomicrograph of malignant gastric polyp showing deep infiltration of anaplastic glandular epithelium.

Fig. 8 (Case 3).—Roentgenogram of the stomach showing the characteristic defect of a polypoid tumor at the pylorus.

Pathology.—The specimen consisted largely of fat, and sections showed in one area a number of tumor cells with indefinite cell outline, granular cytoplasm and oval dark-staining nuclei. These cells were poorly differentiated; many were vacuolated and a few mitotic figures were present. They tended at times to grow into acini, although many formed islands. There was definite invasion of both stroma and tumor cells to the omentum.

Follow-up revealed that this patient died at home, Oct. 25, 1935. No autopsy was performed.

Fig. 9 (Case 4).—Roentgenogram of the stomach showing area of increased radiability representing a probable benign tumor.

Case 4.—A. L. (New York Hospital No. 205103), 29-year-old female, was admitted June 7, 1938, and discharged July 3, 1938. In April, 1937, this patient was admitted to the Rockefeller Hospital with marked hypertension. Examination disclosed a hydronephrotic kidney on the left. In April, 1938, a nephrectomy was performed at the Presbyterian Hospital and the blood pressure fell to 140, systolic. A checkup at the Rockefeller Hospital revealed a low hemoglobin, and a gastrointestinal series showed the presence of a gastric polyp. The patient also recalled having had tarry stools for two weeks prior to admission. There was no epigastric pain or distress. After admission to the New York Hospital with the above history, laboratory examinations revealed hemoglobin, 64 per cent, and red blood count 3,100,000. The stool was positive for occult blood. On June 9, 1938, films and fluoroscopy of the gastrointestinal tract showed a vertical stomach, medium in size and position, orthotonic, with normal peristalsis. There was a circular area of increased radiability in the body of the stomach representing a probable benign tumor (Fig. 9, Case 4). Operation through a left upper rectus incision disclosed a tumor in the stomach attached to the anterior wall, about 4 cm. in diameter. This tumor was excised with a small margin of normal stomach on all sides. Frozen section, however, showed the tumor to be a sarcoma. Since the tumor was in the mid-portion of the stomach a

sleeve resection was done, leaving a margin of 4 cm. on either side of the excised tumor. No regional lymph nodes were seen or felt and there was no evidence of spread to the liver, omentum, or peritoneum.

Pathology.—The specimen consisted of a globular tumor from the stomach, measuring 4½ cm. in diameter. It was covered on both sides by a thin layer of gastric mucosa which showed numerous pits or craters surrounded by elevated, nipplelike thickenings of the mucosa. The bulk of the tumor, however, seemed to lie below this

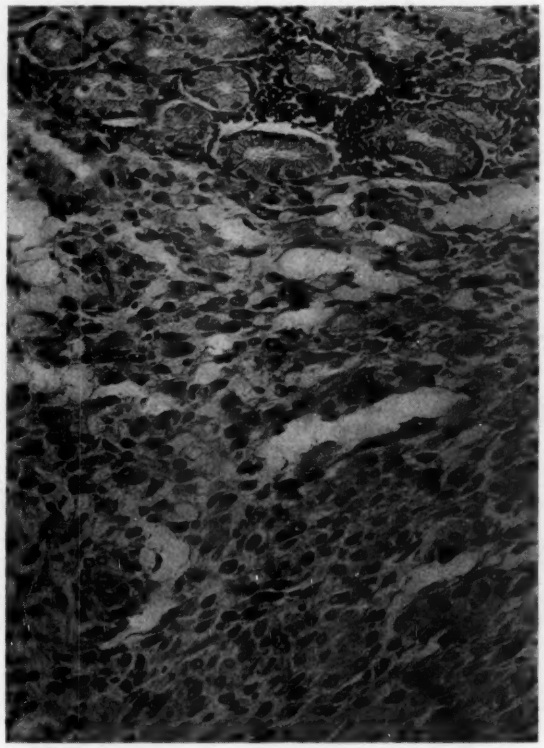

Fig. 10 (Case 4).—Photomicrograph of leiomyosarcoma of stomach showing spindle character of cells and many giant tumor cells.

and to be composed of a light-brown semigelatinous mass of tissue which was chiefly surrounded by the muscular layer of the stomach, although just within this a membranous capsule was apparently quite definitely seen. The tumor had a definitely sarcomatous appearance, and was very soft in consistency, except where it was attached to the gastric musculature, where it was quite firm.

Sections through the gastric tumor, described above in the gross, showed it to be an extremely cellular one. The cells varied markedly in size and shape, many of them being small spindle cells or oval in shape, and others round and epithelioid. Large numbers of giant tumor cells were present. These were undergoing all sorts of mitotic changes. All these cells were growing in a very loose stroma. After staining frozen sections with sudan III, fat cells could not be demonstrated, eliminating the possibility of this tumor being a liposarcoma and marking it as a fairly definite leiomyosarcoma of the stomach (Fig. 10, Case 4).

On July 25, 1939, one year after operation, roentgenologic examination of the stomach revealed the postoperative picture of a sleeve resection with no evidence of recurrence (Fig. 11, Case 4). At follow-up two years after operation, the patient was well and working.

A primary diagnosis of pernicious anemia was made in the following two cases:

Case 5.—A. L. (New York Hospital No. 103630), a woman aged 58 years, was admitted Aug. 8, 1935, with a complaint of weakness. The patient's mother died of pernicious anemia and now one brother is said to be suffering from the same dis-

Fig. 11 (Case 4).—Roentgenogram of sleeve resection of stomach one year after operation. There is no evidence of recurrence.

order. Three years prior to admission to the hospital the patient had suffered from weakness and fatigue. She had had intermittent attacks of glossitis, numbness, and tingling of the toes. Just before admission there had been epigastric distress with a sense of fullness after eating. Liver therapy in the past had given some relief. Examination revealed a subicteric tint to the skin and conjunctiva. The tongue was not particularly smooth. The abdomen was soft and no masses were palpated. There was some loss of vibratory sense over the toes of both extremities. Laboratory examinations revealed no free hydrochloric acid in the gastric contents. There were 4,000,000 red blood cells, with 2+ stippling, macrocytosis; hemoglobin, 95 per cent. Films of the gastrointestinal tract showed a filling defect on the posterior wall near the cardia, about 3 cm. in size. This appeared to project into the gastric lumen, with the base appearing somewhat smaller, and the mass itself giving a pedunculated effect. The impression was that this patient had polyps or a hemangioma of the stomach (Figs. 12 and 13, Case 5).

On August 10, 1935, at operation through a left upper rectus incision, palpation of the stomach revealed the presence of a small tumor arising from the lesser curvature about midway between the cardia and pylorus, with a fairly narrow pedicle, the base of which did not seem to be invading the rest of the wall of the stomach. A wedge-shaped incision was used to excise the tumor and the defect was closed with chromic catgut. This catgut suture line was inverted with mattress sutures of fine black silk in the serosa.

Pathologic Report.—The specimen is a gastric polyp measuring about 3½ cm. by 2 cm. Sections reveal a polyp with a stalk composed of loose connective tissue. The normal gastric mucosa changes its appearance fairly abruptly at the base of the polyp. The goblet cells are few in number and the nuclei are hyperchromatic. No mitotic

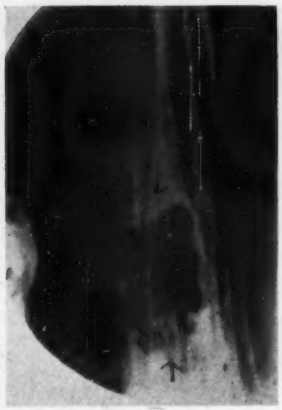

Fig. 12 (Case 5).—Reveals filling defect on posterior wall of stomach near the cardia.

Fig. 13 (Case 5).—Spot film showing filling defect characteristic of benign tumor.

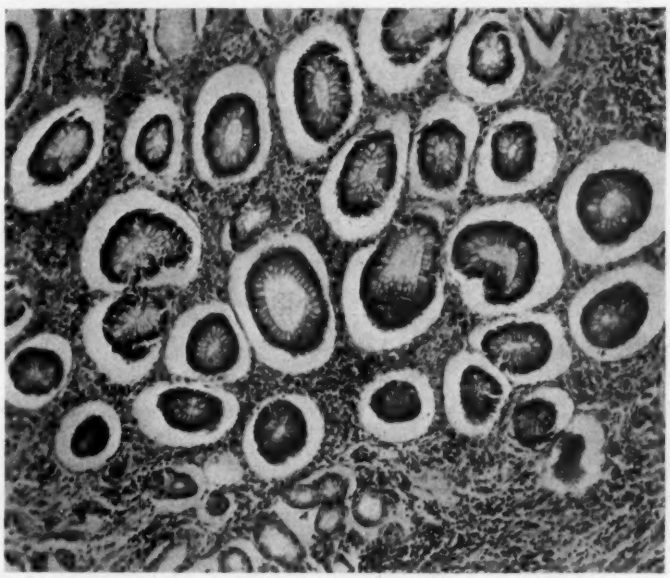

Fig. 14 (Case 5).—Photomicrograph of section of benign polyp of stomach in a patient with pernicious anemia.

figures are seen and all the epithelial cells are arranged in very orderly fashion on the basal membrane without the least tendency to invasion of the underlying tissue. One has the impression, nevertheless, that these cells would become malignant on

very slight provocation. The glands in the polyps are quite well formed (Fig. 14, Case 5).

Following operation, the patient was treated with dilute hydrochloric acid and liver, and discharged from the hospital, Sept. 1, 1935. She came to the outpatient department irregularly for about two years until April 13, 1939, when she was readmitted to the hospital with a true Addisonian anemia, the hemoglobin being 48 per cent, with 1,400,000 red blood cells. Roentgenologic examination of the stomach showed no evidence of recurrence of the polyp. The patient is being maintained on one vial (3 c.c.) of liver extract intramuscularly every three weeks.

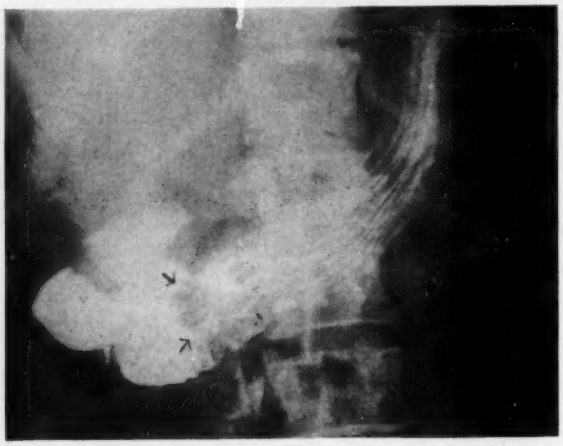

Fig. 15 (Case 6).—Roentgenogram of stomach showing polypoid mass in the prepyloric area.

CASE 6.*—M. R. (New York Hospital No. 61150), a 54-year-old woman, was admitted April 9, 1934, with a complaint of weakness, numbness, and tingling of the toes, with some epigastric distress and belching. For the past twenty years, she has suffered from indigestion, gaseous distention, and vague abdominal pain. Three years ago she developed sore mouth, felt weak, and a gastric analysis revealed achlorhydria, while blood examinations revealed a profound anemia. Under intense liver therapy, she complained of weakness, lack of energy, numbness and tingling of the feet and hands. When liver therapy was stopped there was a tendency for the red blood cell count to drop. Her blood count on admission was 4,000,000, hemoglobin 88 per cent, with a slight variation in the size and shape of the red blood cells. Physical examination revealed a fairly well-developed and well-nourished woman. The papillae on the tongue were good. The abdomen appeared normal. Careful neurologic examination failed to reveal any abnormality. Roentgenologic examination of the gastrointestinal tract revealed a polypoid mass in the prepyloric area on the posterior wall, which was thought to be malignant (Fig. 15, Case 6). She left the hospital on April 25, 1934, to go home to Chicago where operation was to be considered by her family surgeon, who operated upon her in May, 1934. A pedunculated polyp was found near the pylorus on the posterior wall of the stomach. There were four other smaller polyps in this same region. These were excised locally on the assumption that they were benign, and frozen section showed no evidence of malignancy. Permanent sections were diagnosed as chronically inflamed adenomatous polyps, but very early malignancy could not be excluded with certainty.

Since operation her blood count has been maintained at a fairly normal level by liver therapy. She continues to have some abdominal distention and belching after meals. Follow-up x-rays of the stomach have been refused by the patient.

*Courtesy of Dr. Paul B. Sheldon.

In Case 7 there was pyloric obstruction and the x-ray diagnosis was carcinoma of the stomach.

CASE 7.—A. O. (New York Hospital No. 177671), a woman 54 years of age, was admitted Aug. 24, 1937, with a three months' history of epigastric pain associated with vomiting attacks lasting three or four days. Three days before admission she had an attack of abdominal pain with nausea and vomiting, so that even liquid foods were vomited immediately after ingestion. There was a loss of twenty pounds in

Fig. 16 (Case 7).—Roentgenogram of stomach showing the defect in the pyloric region diagnosed as carcinoma, which at operation proved to be a benign polyp.

six months. The patient exhibited typical signs of pyloric obstruction. On physical examination, she was dehydrated and appeared acutely ill. A distinct mass was palpated in the midabdomen at the level of the umbilicus. Her hemoglobin was 70 per cent, red blood count, 3,500,000. X-rays of the stomach revealed an extensive filling defect in the body and antrum. Increased peristalsis was visible and it was felt that there was an extensive carcinoma of the stomach, with involvement of the pyloric region (Fig. 16, Case 7). The patient was given a course of x-ray therapy with some improvement, but the attacks of epigastric pain and vomiting continued, so that sixteen days after admission it was decided to do a palliative gastroenterostomy. At operation the stomach wall was seen to be perfectly normal. A round movable mass was palpated, apparently attached to the posterior wall of the stomach. A large polypoid tumor was delivered through the anterior stomach wall, which had the gross appearance of a benign tumor and was found to be attached to the posterior wall of the stomach by a mucous membrane pedicle. The tumor appeared to have blocked the pylorus. It was excised locally. The postoperative course was smooth and the patient has been perfectly well since the operation.

Pathologic report.—The specimen consisted of a blood-red tumor mass measuring 6 by 4 by 3 cm., symmetrical and coarsely lobular. It was soft and friable and sections revealed innumerable glandular complexes. The cells lining the acini were regular, tall columnar, one layer thick. The surface of the tumor showed small, thin-walled blood vessels. Patches of hemorrhage, areas of ulceration and chronic

inflammation were frequent. Examination of the base of the polyp showed it to be composed entirely of rather dense fibrous tissue which had few small blood vessels. There was no evidence of invasion of the base.

Diagnosis: Adenomatous polyp of the stomach (Fig. 17, Case 7).

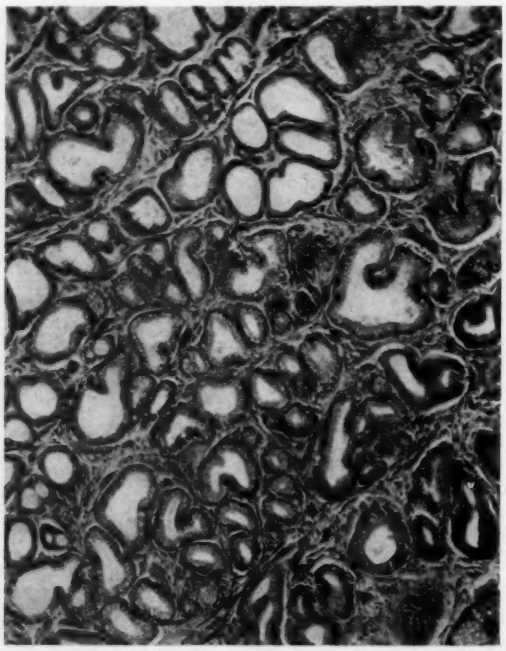

Fig. 17 (Case 7).—Photomicrograph of benign polyp showing innumerable glandular complexes. The cells lining the acini are regular, tall columnar, and one layer thick.

Fig. 18 (Case 8).—Punched-out, circumscribed defect in roentgenogram of stomach typical of benign polyp.

CASE 8.—M. G. (New York Hospital No. 18984), a 52-year-old woman, was treated in the medical clinic from September, 1929, to July, 1931, for chronic constipation and an old paralysis of the tongue and right arm. Gastric analysis revealed no free hydrochloric acid. There was little change in her condition and she was treated at infrequent intervals in the medical clinic until June, 1939, when a gastric analysis again revealed anacidity. Fluoroscopic examination and films of the gastrointestinal tract showed a polyp on the posterior wall of the stomach in the region of the greater curvature (Fig. 18, Case 8). She then was admitted to the hospital, where her hemoglobin was found to be 80 per cent and red blood cell count 4,000,000. On July

Fig. 19 (Case 8).—Photomicrograph of benign polyp showing irregular large glandular structures lined with columnar epithelium.

27, 1939, operation revealed a small polyp about 2 cm. in diameter, easily palpated through the wall of the stomach in the lower portion of the pars media near the greater curvature. This appeared to lie on the anterior wall and was freely movable by virtue of a short pedicle. The remainder of the stomach and duodenum appeared quite normal. A linear incision was made into the stomach between traction sutures and the polyp transfixed through its loose pedicle, which contained only mucosa. The wound in the stomach was closed with mattress sutures of fine black silk.

Pathologic Report.—The specimen consisted of a pink, soft tumor measuring 8 by 9 by 5 mm. On section it was soft and whitish in color.

Microscopic.—Sections of this polyp showed its surface to be ulcerated and covered with purulent material. Immediately beneath this there was a very vascular inflamed fibrous tissue. The main body of the mass, however, was composed of irregular, large glandular structures lined with columnar epithelium. Most of these lining cells were goblet cells secreting mucus. In some areas, however, particularly near the surface, the cells stained more darkly and there appeared to be a few isolated strands which did not clearly form crypts. Amongst these there were fewer

goblet cells. However, one could not consider this as a malignant change, particularly in view of the fact that the inflammation seemed more active about these areas. Close follow-up was advised (Fig. 19, Case 8).

Diagnosis: Gastric adenoma.

The patient did well after the operation and was discharged in about two weeks. She is being followed carefully in the outpatient department, with frequent examinations through the gastroscope. X-rays of the stomach Sept. 21, 1939, showed the rugal markings to be coarse. There was a smooth indentation on the greater curvature on the pyloric end. There were no defects and no evidence of polyp (Fig. 20, Case 8). The last gastroscopic examination, three years after operation, revealed two small sessile polyps less than 1 cm. in diameter. One was near the

Fig. 20 (Case 8).—Postoperative x-ray film of stomach showing no defects and no evidence of polyp.

angularis on the lesser curvature and the other opposite this on the greater curvature. The pyloric ring appeared to be normal. At the last clinic visit in April, 1941, the patient reported that she was working but that she had some epigastric pain and distress. Gastric analysis again revealed no free hydrochloric acid. Hemoglobin was 88 per cent, red blood cell count, 4,200,000.

CASE 9.—This was the one leiomyoma of the entire group. It has already been reported in detail by Conway, in 1936.

F. S. (New York Hospital No. 76807), male, aged 41 years, was admitted to the surgical service Oct. 5, 1934, in a state of shock after sudden hematemesis. Following appropriate therapy, he slowly recovered from the profound anemia. Serial roentgenograms of the gastrointestinal tract on two occasions showed nothing abnormal in the stomach and duodenum. Operation Nov. 15, 1934, revealed a small tumor measuring 2 by 2 cm. in the wall of the lesser curvature of the stomach, 6

cm. from the pylorus. The tumor was locally excised and a posterior gastroenterostomy was done. Microscopic examination of the tumor showed it to be of unmistakable smooth muscle origin. Mitotic figures were not found and for this reason the tumor was classified as a nonmalignant leiomyoma of the stomach. The patient had an uneventful convalescence and was reported to be well nineteen months after operation.

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EXPERIMENTAL PREVENTION OF INTRAPERITONEAL ADHESIONS WITH HEPARIN

Third Report*

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WE PUBLISHED, in 1940, two preliminary papers on the effect of heparin in the prevention of the reformation of experimentally produced peritoneal adhesions.[1, 2] The reported studies included experiments and control observations on fifty-six dogs, indicating an unmistakably favorable effect of heparin. The rationale of the methods and its attendant dangers were fully discussed.

The present report deals with additional experimental work. After the publication of the last paper the entire subject was reopened in the laboratory and restudied with greatly enlarged experimental and control series. This step seemed important because of the danger that more skillful operative handling of adhesions with added experience might have weighted the results in favor of heparin. The new experiments total twice as many as those previously reported. The present paper, recording more than 170 experiments, consolidates the older material with the later results.

METHODS

At the start of the investigation, clinical conditions were mimicked in the production of peritoneal adhesions by creating an infectious peritonitis from fecal contamination caused by an intraperitoneal appendicostomy. The mortality from this procedure due to acute suppurative peritonitis was about 50 per cent; this wastage of animals was later avoided by employing mechanical damage to create adhesions. As the results of the two methods are approximately the same, no attempt will be made to divide the experiments reported according to the etiology of the adhesions. About six weeks after the operation to create adhesions (either by contamination or scarification), the abdomen was reopened, the adhesions counted and, in the latter half of the study, also measured. Complete separation of all adhesions was then carried out largely by sharp dissection. After effecting complete hemostasis, the abdomen was closed. At this stage the animals were divided into

*The material presented here formed a part of the Hodgen lecture delivered by the senior author on invitation of the St. Louis Surgical Society, St. Louis, Mo., Jan. 13, 1942.

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two groups, experimental and control. The former were given heparin intraperitoneally at the close of the operation and in varying dosages by abdominal paracentesis thereafter. A series of dosage experiments, previously reported,[2] indicated that for full effect heparin must be given for at least three days after separation of adhesions, and all of the experiments reported are from animals so treated. The control group was further subdivided. One subgroup received no auxiliary treatment, and one subgroup each was treated with corresponding amounts of normal saline solution, amniotic fluid* and papain solution.† After a further period of two to six weeks, at a third laparotomy, the number and extent of re-formed adhesions were recorded. In a series of ten experiments, repeated division of adhesions followed by heparin administration was carried out in individual animals.

RESULTS

The results (Fig. 1) have been remarkably consistent throughout. It is clear that under the described conditions of experimentation, heparin has proved considerably more effective in the dog than any other agent. In the controls more adhesions re-form than are divided even with the use of such drugs as amniotic fluid and papain, which seem to possess no advantageous action. With the use of heparin, however, the average re-formation rate is only 35 per cent of the number divided.

The gross data were broken down in an attempt to determine whether the number of adhesions divided influenced the percentage result. Those heparin animals in which six or more adhesions were divided presented approximately the same percentage of recurrence as those with fewer adhesions.‡

In the earlier portion of the study heparin from the Connaught Laboratories was employed exclusively. After extensive testing on blood coagulation both in vitro and in vivo, we later shifted to Liquaemin, a domestic heparin.§ The preliminary studies indicated almost equal effectiveness and equal nontoxicity of the two products. When the results of intraperitoneal employment were divided according to the product used (Fig. 2), there was a slight difference in favor of the Connaught material which averaged 30.7 per cent of re-formation as compared to 41 per cent in a smaller series of Liquaemin experiments. This difference is believed to be within the limits of error of the necessarily crude method of quantitative measurement, although it corresponds roughly to the differences observed in the effect on blood coagulation of the two products.

The results of repeated division of adhesions indicate that with the use of heparin progressive diminution of the number occurs. When the

*Amfetin, supplied by Eli Lilly and Company.

†Supplied by Parke-Davis & Co.

‡This statement takes precedence over the statement of Boys (reference 4, p. 144) which was made on calculations from a smaller number of observations.

§Furnished by the courtesy of Hoffmann-LaRoche, Inc.

original heparin animals were subjected to a second division of adhesions followed by heparin treatment, the final number of re-formed adhesions was only 24 per cent of the number at the beginning of the experiment as compared to 168 per cent in controls (Fig. 3). In three of the ten heparinized animals the abdomen was completely free of adhesions, in one instance when ten adhesions had been originally divided. In three other instances, only one adhesion remained and in two instances only two. With the omission of the only unfavorable experiment in this group, the average final re-formation rate for the remaining nine was 17 per cent.

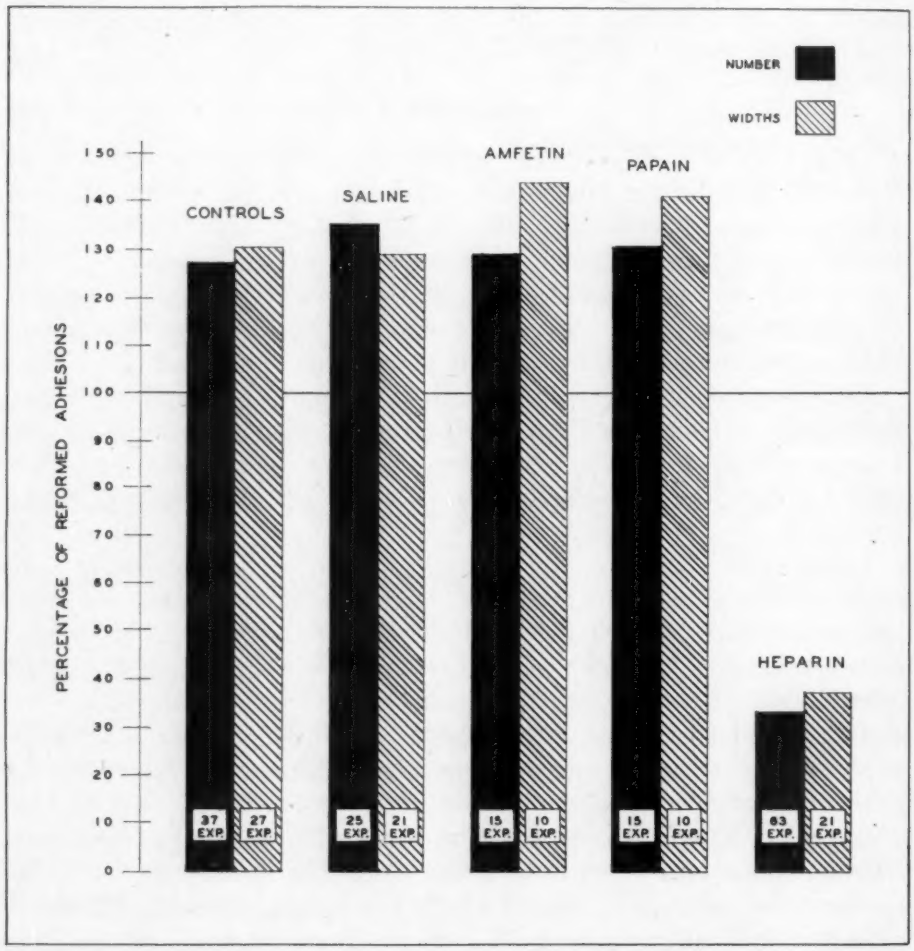

Fig. 1.—Consolidated results of all experiments and controls including data already published.[1, 2] Three-quarters of the data presented here are new. The blocks represent the average percentage re-formation rate of divided adhesions.

Since especial care has been taken with hemostasis, hemorrhage has ceased to be an experimental hazard. There have been as many as 101 consecutive intraperitoneal applications of heparin after the division of adhesions without bleeding.

DISCUSSION

Although there have been rare individual failures of heparin effect in the course of this study, the average results including such failures have been remarkably uniform. The data reported above seem to indicate that heparin is unquestionably effective in the dog in diminishing the number of adhesions re-formed following division.

The results of this study strongly indicate the possibility that heparin may be made to play a role in the process of inflammation, particularly in its later stages. The prevention of fibrin formation in an exudate by heparin may modify the production of granulation tissue. The implications of this possible mechanism are twofold. In the first place, as in the present experiments, the result may be a quantitative diminution of scar tissue. From this point of view the method may be practically applicable to many conditions in which scar tissue creates a diseased state in itself. As previously suggested,[1] such conditions include adhesions within joints, tendon sheaths, and the pericardium as well as the peritoneum.

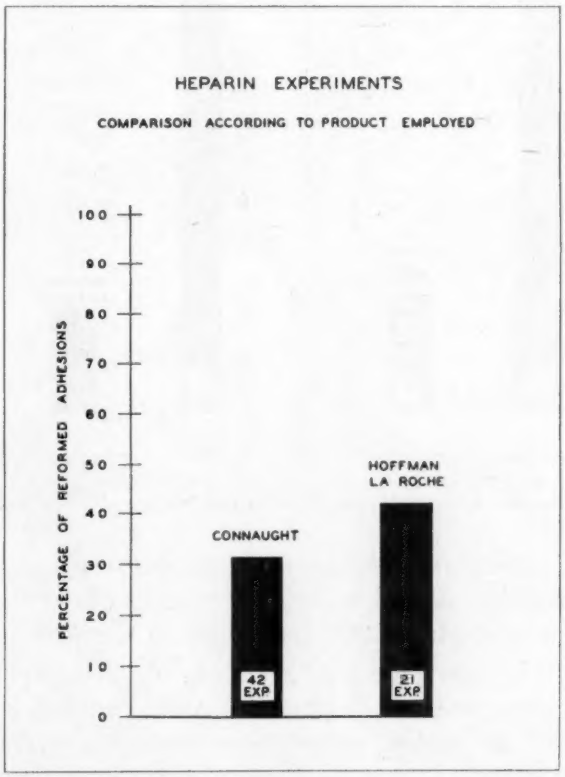

Fig. 2.—Comparison of the effectiveness of two brands of heparin in the prevention of the re-formation of divided adhesions. The difference shown is probably within the limit of error of the method of measurement.

In the second place, the prevention of the development of granulation tissue which is a constant accompaniment of the healing stage of advanced inflammatory processes implies the retardation of recovery.

Careful quantitative studies are needed to determine whether wound healing is retarded and whether infections are prolonged by the exhibition of heparin.

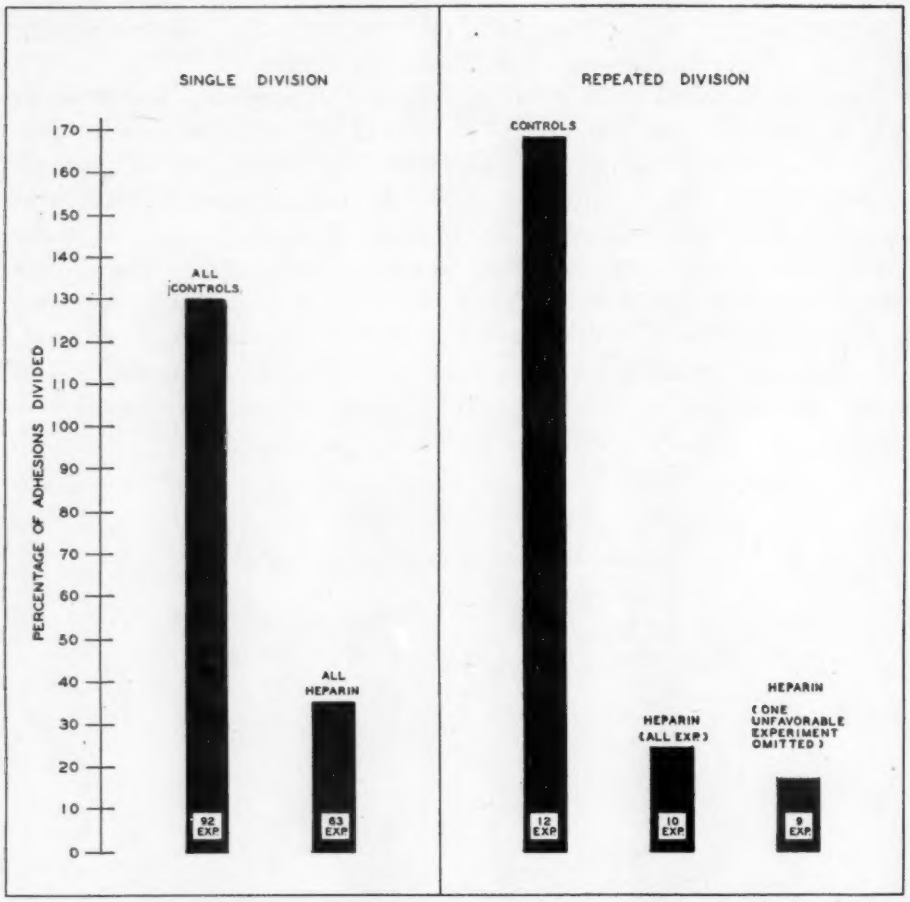

Fig. 3.—Comparison of the re-formation rate following repeated division of adhesions with and without intraperitoneal heparin administration.

Finally, the experimental results recorded above are so striking and the one danger of the method, namely hemorrhage, is so clearly defined, that the clinical application of the principle in the prevention of peritoneal adhesions is now considered justified. A recent report[3] presents the results of intraperitoneal heparinization in fourteen clinical cases. Since the preparation of that report there have been several other cases without complications. Of the fourteen cases reported, one patient died of intraperitoneal hemorrhage as the result of unmistakably improper choice of case coupled with imperfect postoperative observation. For details of the clinical application including the indications, the contraindications, the technique, and the precautions, it is urged that the clinical report referred to[3] be consulted.

CONCLUSIONS

1. Heparin administered intraperitoneally definitely diminishes the re-formation rate of divided adhesions in the experimental animal.

2. The extension of the principle to other structures in which fibrosis may be harmful is suggested.

3. The clinical application of the method in the peritoneal cavity is justified under indications and contraindications discussed elsewhere.

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EFFECT OF THERAPEUTIC BLOOD LEVELS OF SULFANILAMIDE AND SULFADIAZINE ON WOUND HEALING

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(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

THE extensive use of the sulfonamides to prevent and control infection in surgical wounds has raised the question of the possible effect that these drugs may have on wound healing. Several papers have already been published on this subject. It seemed that with the widespread use of these compounds in civil and military practice, and with the differences in opinion which have arisen, the subject might be investigated further under different environmental conditions. We have studied the tensile strength of healing wounds in dogs receiving sulfanilamide and sulfadiazine.

METHOD

Mongrel dogs were selected as the experimental animals. The tensile strength of the wounds and histologic studies were used as the indices of healing. Skin, fascia, and stomach wall were the tissues which were studied. Since hypoproteinemia impairs wound healing, as has been shown by Thompson, Ravdin, and Frank,[1] serum protein concentrations were determined at operation and at the time the dogs were sacrificed, using the method of Barbour and Hamilton.[2] It should be mentioned that the normal serum protein level of dogs is somewhat lower than that of man, being about 6.0 Gm. per cent.

An adequate intake of vitamin C is also necessary for normal wound healing (Lanman and Ingalls[3]). This was insured by giving all the animals throughout the experiment a diet ample for all nutritional needs, and in addition, those animals receiving chemotherapy were given 10 mg. of ascorbic acid daily with their sulfonamide drug. The animals were weighed at the time of operation and again at the time they were sacrificed.

Adequate therapeutic drug levels were maintained in the experimental group of animals by the administration of the sulfonamides directly into the stomach by means of a stomach tube. In the case of the sulfanilamide group, sulfanilamide powder in dosages of 3.0 Gm. daily were given in three divided doses, eight hours apart. The drug was begun three days preoperatively and continued daily until the animal was sacrificed. The sulfadiazine dogs were given an initial dose of 0.5 Gm.

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and subsequent doses of 0.25 Gm. per kilogram of body weight per day. This drug was also begun three days preoperatively and continued until sacrifice. The blood levels of the dogs were determined by the method of Marshall and Cutting[4] on the day of operation and on the day they were sacrificed. The control animals received no sulfonamides.

Sixteen dogs were used in the experimental group in the sulfanilamide studies. The animals were sacrificed at selected postoperative intervals, namely four, five, six, seven, eight, nine, ten, eleven, twelve, and thirteen days postoperatively. In the sulfadiazine studies there were fifteen animals in the experimental group. These were sacrificed on the third, fifth, seventh, ninth, eleventh and thirteenth postoperative days. The control group consisted of sixteen dogs sacrificed postoperatively at intervals of three, four, five, seven, eight, nine, eleven, and thirteen days. The sulfanilamide, sulfadiazine, and control animals were all subjected to the same operative technique.

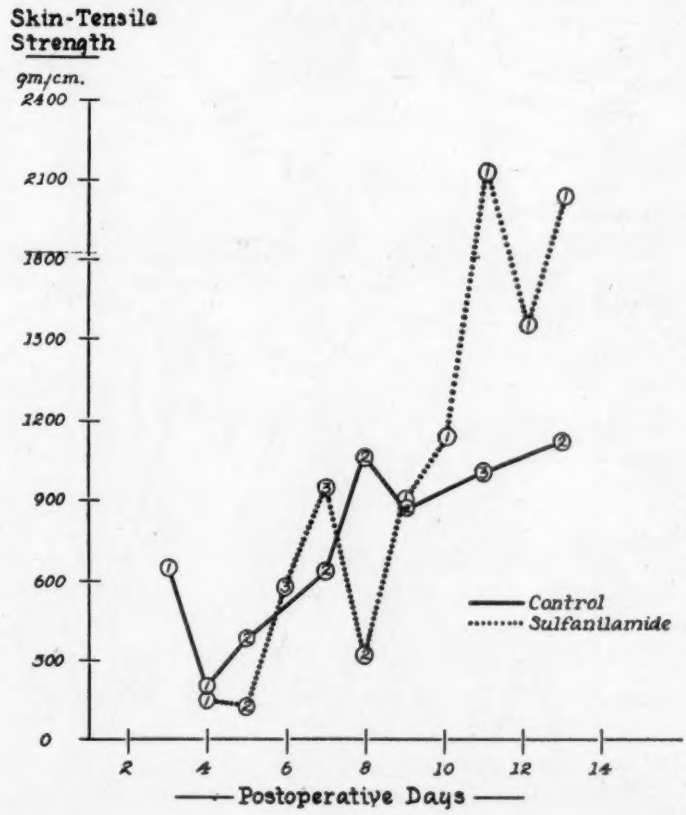

Fig. 1.

The skin of the right upper abdominal quadrant was used for these studies. Under aseptic technique a transverse incision about 2 cm. in length was made through the skin at this site. After careful hemostasis the incision was promptly closed with fine silk interrupted sutures.

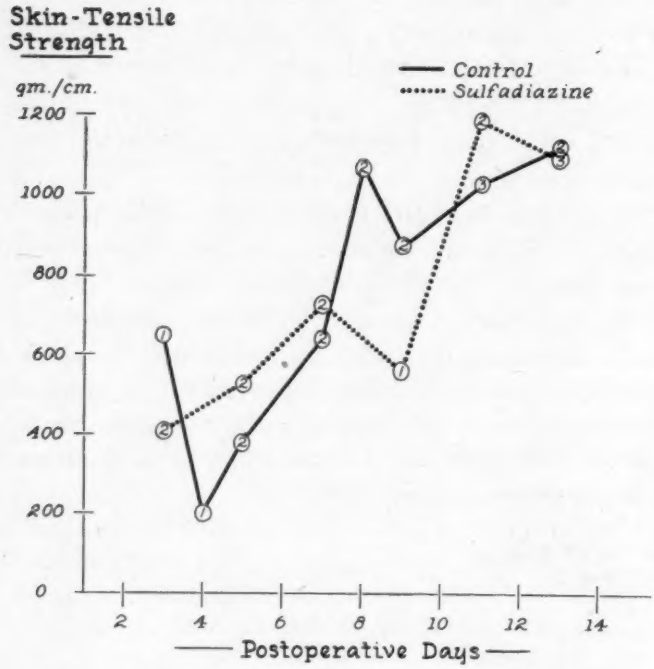
Skin-Tensile Strength
gm./cm.
Control
Sulfadiazine
1200
1000
800
600
400
200
0
2
4
6
8
10
12
14
Postoperative Days

Fig. 2.

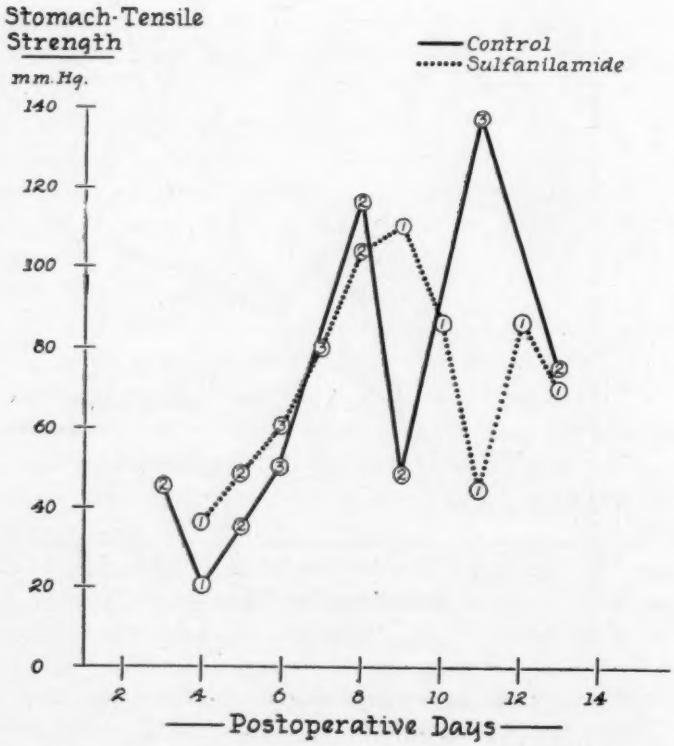
Stomach-Tensile Strength
mm.Hg.
Control
Sulfanilamide
140
120
100
80
60
40
20
0
2
4
6
8
10
12
14
Postoperative Days

Fig. 3.

No dressing was applied. On the day of sacrifice, the skin sutures were removed and an area two inches square was measured around this incision. This area of skin was dissected free from the underlying subcutaneous tissue, pinned on a wooden block to its original size and shape, and a piece of the tissue including 1 cm. of the wound was stamped from the square by means of a steel die. The tensile strength of this piece of tissue was measured by the tensiometer method of Meade.[5] This method provides a measure of the number of grams required to disrupt an area of the wound 1 cm. in cross section. Histologic sections were prepared from a separate section of the wound.

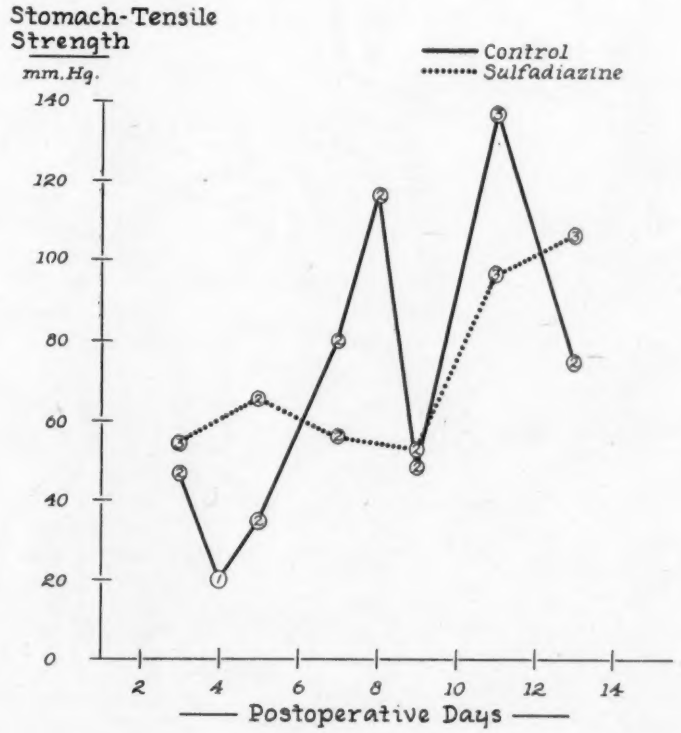

Fig. 4.

The stomach was approached through a midline abdominal incision. After exposure of the stomach an intestinal clamp was applied, and an incision exactly 2 cm. in length was made through the anterior wall of the cardia. Care was taken to avoid the larger vessels. The incision was promptly closed with two layers of interrupted plain 000 catgut. The first layer included mucosa and submucosa, and the second included muscularis and serosa. Care was used to make certain that there was no bleeding from the wound after the gastric clamp had been removed. The peritoneum, fascia, and skin of the abdominal incision were closed by means of fine continuous silk sutures. On the day of sacrifice the stomach was removed, and the tensile strength of the

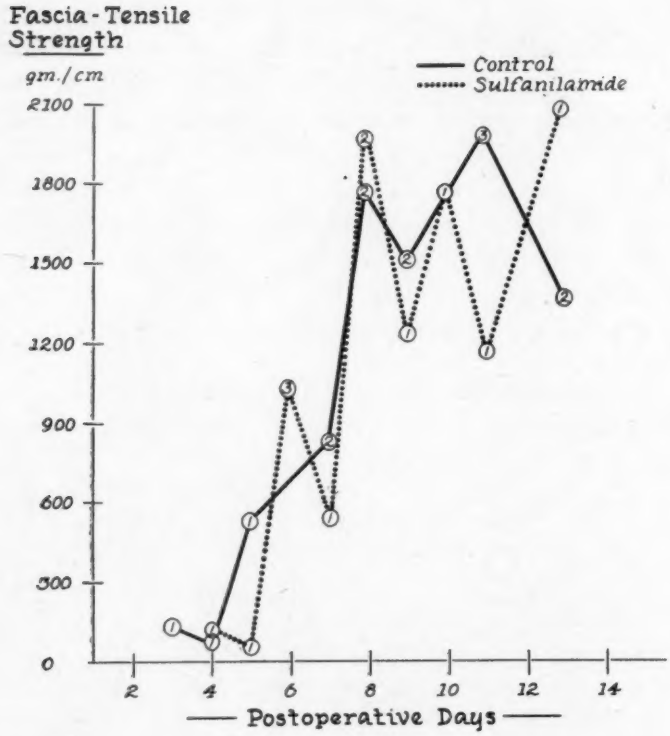
Fascia-Tensile Strength
gm./cm
2100
1800
1500
1200
900
600
300
0
2
4
6
8
10
12
14
Postoperative Days
Control
Sulfanilamide

Fig. 5.

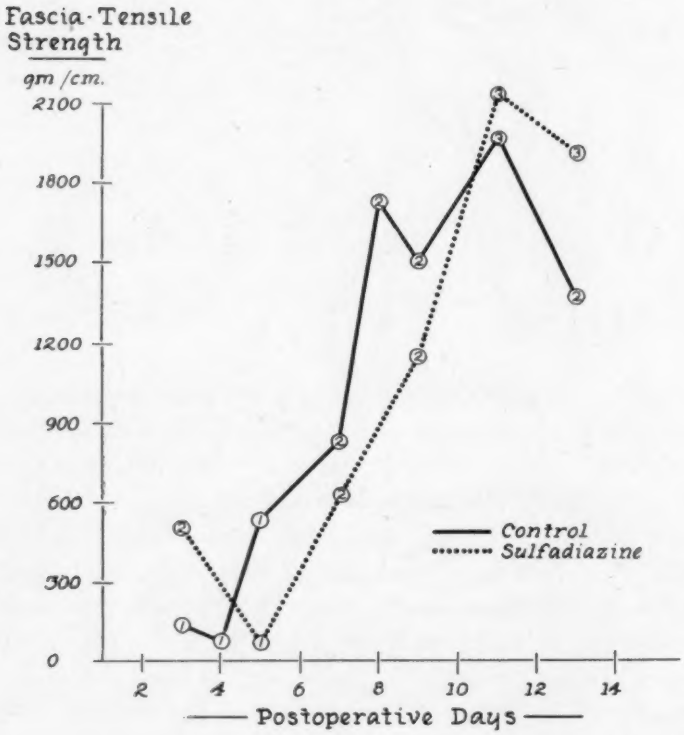
Fascia-Tensile Strength
gm/cm.
2100
1800
1500
1200
900
600
300
0
2
4
6
8
10
12
14
Postoperative Days
Control
Sulfadiazine

Fig. 6.

wound was then determined by the air pressure inflation mercury manometer method of Harvey and Howes.[6] Histologic sections were also made of these wounds.

The upper third of the left anterior rectus sheath was exposed and a transverse incision approximately 2 cm. in length was made through it and promptly closed with plain 0 catgut by interrupted sutures. Careful hemostasis was observed. On the day of sacrifice an area two inches square was measured around the wound site. This area of fascia was dissected free from the underlying muscle and the tensile strength measured in the same manner as that of the skin. Histologic sections were made of the wound site.

Fig. 7.—Control dog, No. 337. Photomicrograph of section through stomach incision eleven days postoperatively. Complete repair of mucosa can be seen. Muscular layers are healed by fibroblastic proliferation.

The operations were performed under either sodium amytal anesthesia, 50 mg. per kilogram of body weight administered intraperitoneally, or by the open-drop ether method. An aseptic technique was employed for all operations and care was used to obtain perfect hemostasis. Trauma was minimized. The animals were sacrificed by giving an intracardial injection of chloroform. Careful handling of the wound

tissue during the manipulations necessary for tensile strength determinations was used to avoid any artificial disruption of the wounds.

Fig. 8.—Dog No. 277, given sulfadiazine. Photomicrograph of section through stomach incision eleven days postoperatively. Complete repair of mucosa can be seen. Muscular layers are healed by fibroblastic proliferation.

RESULTS

As shown in Figs. 1 to 6, there was found to be no appreciable difference between the tensile strength of the skin wounds in those animals receiving sulfanilamide and sulfadiazine, from those of the control group. Wherever possible, two or more dogs were used to determine the average for each day of sacrifice. It should be pointed out that our tensile strength figures are a little lower through the experiment than those given by other methods because we stretched the skin to its original size and shape before cutting the specimen. Other workers have not done this, allowing the tissue to contract before cutting the specimen, and thus including more actual tissue in their specimen than we did. Histologic studies of some of these skin wounds showed some inflammatory reaction of varying degrees as evidenced by the presence

of polymorphonuclear leucocytes, fibrin, and detritis. This was due partly to the trauma of operation and partly to postoperative trauma as no dressings were used. The extent of epithelization varied somewhat in different dogs in both the experimental and the control groups on comparable days.

The results of the tensile strength studies of the stomach are expressed in millimeters of mercury and no significant differences were found between those animals receiving sulfonamide and those used as controls. Little difference was found on histologic examination of the wounds in the dogs receiving sulfonamide and in the control dogs of comparable postoperative days (Figs. 7 and 8). Mucosal regeneration was, as a rule, complete in both sets of dogs from the seventh day. The submucosa, muscularis, and serosa were also fairly well healed by fibroblastic proliferation at that time. There was no evidence of inflammatory reaction, edema, or hematoma.

The tensile strength figures for fascial tissue in control wounds closely paralleled those of the sulfonamide wounds. Microscopically the healing appeared the same in both groups of animals. Inflammatory changes were not seen as often in these sections as in the skin group. This is accounted for largely by the fact that the skin wound was exposed to external bacteria and trauma during the healing period.

In all six graphs there can be seen occasional wide variations in both directions from the general trend of the curves. These variations are seen in both control and experimental animals and have been noticed and commented upon in studies made by other workers.[10]

The sulfanilamide concentration varied in the treated group between 2.3 and 30.8 mg. per cent, with an average of 19.7 mg. per cent of those levels taken approximately eight hours after the last administration of the drug. The sulfadiazine levels were between 6.7 and 36.4 mg. per cent, with an average of 17.7 mg. per cent. The specimens for sulfadiazine levels were taken approximately twenty-four hours after the last drug administration.

The body weight of the dogs was satisfactorily maintained and only two of the forty-nine dogs had serum protein concentrations below normal, both of these being 4.7 Gm. per cent. Neither one of these two animals showed significant variations from the final tensile strength curves.

DISCUSSION

Our results seem to indicate that sulfanilamide and sulfadiazine in adequate concentrations in the tissue fluids do not retard or inhibit wound healing. The curves of healing of the control animals as compared to those of the experimental groups are practically identical and histologic studies revealed no striking differences. This is true of skin, fascia, and stomach wall in dogs.

An early report by Bricker and Graham[9] on the effect of oral administration of sulfanilamide on the stomach wall of dogs at the third, fifth, and seventh postoperative days seemed to indicate that this drug had an inhibiting effect on wound healing. Their experiments did not extend over all the phases of wound healing, going up only to the seventh postoperative day. Taffel and Harvey,[7] working with the same drug and studying gastric wounds in rats, found no change in the rate of healing.

Key, Frankel, and Burford,[8] using local sulfanilamide implantation in muscle, fascia, and subcutaneous tissue of dogs, obtained findings similar to our own. Recently Harbison and Key,[10] using sulfanilamide, sulfathiazole, and sulfadiazine implanted locally in wounds in rats, found no significant retardation of healing.

Our findings confirm and extend the observations of recent workers in this field who have shown that sulfonamides have no inhibiting effect on wound healing, when adequate concentrations in the blood are maintained and when caking in the wound is prevented.

CONCLUSIONS

1. Sixteen dogs fed sulfanilamide by intubation and sixteen control dogs were studied from the standpoint of tensile strength and histologic picture of surgical wounds made in the stomach wall, the fascia, and the skin at four-, five-, six-, seven-, eight-, nine-, ten-, eleven-, twelve-, and thirteen-day intervals. No appreciable difference was found.

2. Fifteen dogs fed sulfadiazine were studied in a similar manner at the third, fifth, seventh, ninth, eleventh, and thirteenth postoperative days and no significant difference was found.

3. Therapeutic sulfanilamide and sulfadiazine blood levels do not inhibit wound healing.

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A STUDY OF THE PHYSICAL FACTORS CONCERNED IN INFLAMMATION

I. The Role of Hydrostatic and Physicochemical Forces in the Establishment of Certain Equilibria*

Carroll J. Bellis,† M.D., Ph.D., Minneapolis, Minn.

INTRODUCTION

General Definition of the Inflammatory Process

Adami[2] has characterized inflammation as the reaction of irritated or damaged tissues which still retain vitality, being essentially a process of adaptation of the organism. It consists of a series of changes locally manifesting the attempt at repair of actual or referred injury to a part. Cohnheim[21] considered inflammation as a process to reduce the harmful consequences of injury, and Opie[47] defined inflammation as a process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. Excellent descriptions of the inflammatory process have been recorded, and each observer has attempted to rationalize the clinical and microscopic appearance of the inflamed tissues on the basis of the underlying histology. Virchow emphasized that the increased metabolism of the inflamed area was due to the increased nutritive demands of the involved tissues.

Capillaries in inflammation.—William Harvey[35] noted the many circumstances which altered the blood flow, and Burke attempted to explain the inflammatory process primarily as a result of capillary dilatation. Using a plethysmograph with photographic recording, Burton[16] showed that from full constriction to full dilatation there was an increase from 5 c.c. per min. per 100 Gm. tissue to 60 c.c. per min. per 100 Gm. tissue.

After Bayless and Gaskell[32] had shown that carbon dioxide is a capillary dilator, Findlay[29] stated that histamine-like substances liberated at the point of injury caused a local dilatation of the small vessels and arterioles and an increased permeability of the local vessel walls. This same conception has been held by others (Dale and co-workers[23]), and Harris showed that vasodilatation in the submaxillary gland may be produced by the collection of metabolites and that the production of osmotically active substances greatly increased filtration.

Although Ricker and Regendanz[52] had maintained that the capillaries in inflammation are not more permeable and that the composition of the edema fluid could be explained by increased intracapillary pressure,

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other observers insist that the capillaries are rendered highly permeable during inflammation. Still other investigators have explained the apparent increased permeability as being due to capillary stasis and opening of arteriovenous anastomoses (Clark and Clark[20]) with establishment of a greater capillary bed.

The papers of Sir Thomas Lewis[40] record his experiments on capillary reactivity, particularly as regards wheal formation. In his words, ". . . there exists in the skin a single and organized mechanism of defense against injury of all kinds and . . . the agent which alarms the garrison and mobilizes the first forces of this defense is a chemical agent derived from the tissues . . . being independent of higher centers of organization (nervous) and of distribution (vascular)."

Diapedesis.—With the dilatation of capillaries in the inflammatory field and the resulting slowing of the stream, margination and emigration are coincident phenomena. Arnold[4] insisted that diapedesis took place through preformed stomata in the capillary wall. The French school strongly believed in diapedesis as an active process induced by contact of the capillary wall with bacteria or their products. Fischer[30] led a school which did not believe in capillary stomata. He showed that erythrocytes could pass through gelatin by gravity or pressure without leaving holes or any other traces, just as mercury will pass through solidified gelatin.

Abramson[1] was probably the first to investigate the intimate relationships between electrostatic charges on the blood cell surfaces and that on the capillary walls. Although it had been known for a long time that dead or living bacteria or their products were strongly chemiotactic, it was not until the studies of Falk and his co-workers[28] that the electrophoretic potential of bacteria and leucocytes was quantitated.

The brilliant papers of Abramson on the alteration of electrostatic charge induced by inflammation should be reviewed by every student of the subject. Briefly, it appears that normally blood cells (Bellis and Scott[10]) and capillary membranes possess a negative charge (thermodynamic and electrokinetic potentials). In inflammation, the potential on the capillary is reduced causing attraction of leucocytes (margination), diapedesis resulting from the increased potential difference between the colloidal micelles in the tissue spaces and the leucocytes. Both the thermodynamic and electrokinetic potentials on the leucocyte are greater than on the erythrocyte because of the greater size of the leucocyte; hence, a much greater reduction of potential on the capillary is necessary to produce a margination and migration of erythrocytes. In severe inflammations even this takes place.

Permeability of Capillaries to Protein

Although the glomerular ultrafiltrate is normally protein free, the capillary wall in other parts of the body is permeable to protein

(Drinker and Field;[25] Conklin;[22] R. Magnus;[42] Churchill, Hakazawa, and Drinker;[19] Peters;[49] and Böhm[12]).

Lymph formation and the character of exudates have received considerable treatment in the literature, and Meyer[45] has adequately discussed the origin and removal of edema fluid. It is generally conceded that subcutaneous lymph and plasma are nearly identical in chemical composition except for proteins and substances (phosphorus and calcium) combined with protein (Underhill and co-workers;[62] and Drinker and Field[25]). Subcutaneous lymph in the human being has been found to contain as high as 3.5 per cent protein, the albumin-globulin ratio being the same as that in the corresponding blood plasma.

The fibrinogen content of blood plasma in acute infections is markedly increased and this may account for the gelatinous matrix of the inflammatory field. This exudate, when rendered cell free, is far more bactericidal than is the blood serum of the same animal, but it appears that leucocytic products are largely responsible for this activity.

Regional Lymph Flow

In the horse, a volume of lymph equal to that of the blood may be obtained in twenty-four hours. Starling[57] showed that in order to get any lymph at all for study in the normal animal, one has to knead or passively move the limb. This probably increases the protein content so that "normal" figures are inaccurate. In edematous tissues, however, the connective tissue tends to hold the lymphatics open so that there is a greater lymph flow, the oncotic pressure of the blood opposing the capillary filtration pressure. Exercise, heat, and inflammation increase the lymph flow and pressure (McMaster and collaborators[43]), and, in fact, if mildly inflamed, lymphatics will allow the diffusion of otherwise indiffusible dyes through their walls.

From a clinical standpoint, it is interesting that Parsons and McMaster discovered that pulsatile perfusion of rabbit ear blood vessels caused fifteen to twenty times more rapid lymph flow than when constant blood pressure was applied, despite the fact that in many instances less blood flow per gram of ear occurred. Edema sometimes developed during the course of a pulsatile transfusion, concurrent with an enormous increase of lymph flow, although the volume of blood perfused was relatively small.

Statement of the Problem

Although the sulfonamides at present begin to hold out some hope in the stemming of spreading infection, there has yet appeared no immunologic agent to unburden the surgeon of his struggle with this type of condition. As Wangensteen[63] has pointed out, the surgeon has learned that incision of extending areas of phlegmon and cellulitis does not stem the spread of infection, that, in fact, such procedures do harm. Whether such an infection be in the soft tissues of the arm, leg, brain, or lung, the surgeon must restrain himself and support the natural

defenses of the body, withholding actual surgical intervention until signs of localized suppuration are evident. Then, and only then, should incision and drainage be established.

Formerly, therapy was direct at reduction of the effects of inflammation, but more recently it was suggested by some pathologists that the accompanying swelling was useful and helped fix the infection locally and lessened the tendency to centripetal spread. A boil, so to speak, was small price to pay for protection from pyemia. Mindful of this Bier[11] sought to increase the heat and swelling attending infection by application of heat, by obstructing the venous return, and by cupping. Noetzel believed that there is a current of tissue fluid established by Bier's hyperemia, the new transudate being bactericidal and the hyperemia stimulating fibrosis.

Undoubtedly, inflammatory exudate possesses immunologic properties; yet, the impression cannot be avoided that tense edema is harmful, the factor limiting the transudation being the distensibility of the tissues. It has been observed clinically that elevation, immobilization, and avoidance of heat accelerate the clearing up of infection and are accompanied by striking relief of pain.

The stimulation to investigate the underlying physical factors in inflammation came from these clear-cut clinical observations, and an attempt was made to correlate these factors with the treatment. It was expected that exact quantitation of certain values would not be possible, nor would all the factors be known. However, it was necessary that certain quantitative as well as qualitative data (as observed in the clinic) be obtained under experimental control.

To this end, the relation between position of an extremity and the systolic blood pressure distally was determined, since elevation is known to reduce the hydrostatic force of the systolic blood pressure in direct ratio to the degree of elevation of the part. What effect elevation has on the systolic pressure should be reflected in the skin surface temperatures. It was, therefore, proposed to measure these temperatures in the horizontal position and after elevation of the extremity.

Tissue swelling occurs through the agency of increased capillary permeability and intracapillary pressure. The increasing tissue pressure causes venous compression and augmented venous pressure with a further increase in intracapillary pressure. This cycle augments further filtration of fluid into the inflamed area. It was obvious that in order to evaluate the effects of tissue tension, normal tissue tensions and then the tensions at inflammatory sites had to be determined.

Having obtained information as to the relation of position to blood flow and the degree of tissue pressure exerted in inflammation, it followed that the volume of the inflamed extremity must be increased over that of the normal. The very effect of gravity on a normal extremity was questioned and studied and the volume differences in various types of inflammations were measured.

Heat aggravates filtration through both normally and abnormally permeable capillaries, and therefore the temperature of the skin should be a reflection, in part, of the amount and rate of capillary filtration and swelling. Therefore, skin surface temperatures were measured in normal extremities and in many types of inflammations. At the same time, the abnormal capillary permeability was studied by determining the specific gravity and protein content of the edema fluid.

Having made these clinical observations, it was determined to alter and control the conditions in the experimental animal, to establish, if possible, a predictable basis for evaluating certain of the factors. It was proposed to determine, in the same animal, the oncotic pressure exerted by the blood on one hand and the tissue fluid on the other, as well as the capillary filtration pressure and the resistance of the tissues to distention. Special observations were intended of the volume changes occurring in experimentally inflamed extremities, the pH of the edema fluid, and the relation of the edema fluid protein concentration to plasma protein concentration. The rate of lymph flow in the lymphatics draining an inflamed area should be different from that draining a normal area and it was planned to study the rate of this flow.

Finally, the results obtained by immobilization and elevation of inflamed extremities were evaluated by a questionnaire sent to a large series of patients so treated.

METHODS AND EXPERIMENTS

Position and Blood Flow in the Patient

Arterial Blood Pressure.—In twelve individuals the radial systolic blood pressure was determined with the arm (1) horizontal, that is, in the plane of the horizontally lying individual; (2) elevated perpendicular to the body; and (3) dependent perpendicular to the body over the side of the bed. These results were then tabulated.

Skin Surface Temperatures.—The skin surface temperatures of a finger in each of five normal individuals were determined in the horizontal position and after one hour of elevation perpendicular to the horizontal, using the apparatus of Bellis and Cook.[9]

In each of six men, the skin surface temperatures along both lower extremities were determined with both extremities in the plane of the horizontal trunk, and after having maintained the right lower extremity elevated for about twelve hours at an angle of 60°. The skin surface temperatures of another individual were determined before and after twelve hours in semi-Fowler's position.

Tissue Tensions in the Patient

Normal Tissue Tensions.—Landerer[38] appears to have been the first to consider the importance of tissue elasticity or tension in counterbalancing capillary filtration. He used a direct manometric system with a

needle inserted into the tissues. The apparatus we used for direct measurement is shown in Fig. 1, and consists of a needle assembly which is connected to a pressure bulb manometer. A little saline solution is aspirated to any convenient level in the glass adapter which has a capillary bore. The needle is then inserted into the tissue to be studied and the needle assembly connected to the bulb and manometer by means of the cock. Pressure is then made on the rubber bulb, using the screw clamp, until the saline meniscus in the capillary just starts to descend. The manometer is then read, corrected for capillarity (about 2 to 3 cm. of saline solution for a 0.5 mm. capillary bore) and the reading assumed to be the tissue tension, really the resistance to distention.

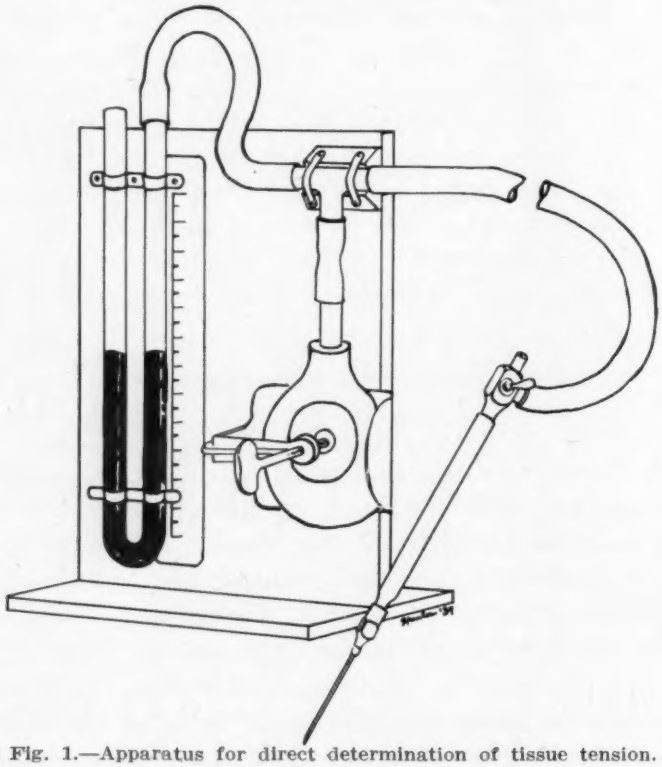


Fig. 1.—Apparatus for direct determination of tissue tension.

In a series of 103 patients visiting the medical outpatient clinic, the subcutaneous tissue tensions in the dorsum of the hand and midthigh were determined.

Since it is known that the intramuscular pressure is higher in contracted than in relaxed muscle, we measured the intramuscular pressures in twenty-eight ambulatory patients and twenty-six patients who had had several days of bed rest. The muscles used were the biceps brachii, deltoid, quadriceps femoris, and the tibialis anticus.

Tissue Tensions in Inflammation.—In a series of fractures, the intramuscular and subcutaneous pressures were determined. In twenty-six

cases the pressures were determined before immobilization, and in 22 cases the intramuscular pressures were determined after partial immobilization. The pressures were also obtained in a shorter series of miscellaneous affections.

In a series of twenty cases of inflammations involving either an upper or lower extremity in which the skin surface temperatures were also measured, the tissue tensions at several corresponding points in the affected and unaffected extremities were determined.

Position and Volume Changes in the Human Being

It has been known for a long time that quiet standing leads to hemoconcentration, manifested by an increase in the specific gravity of the blood and plasma and decrease in circulating blood volume (Böhme;[13] Harrop and Waterfield;[34] Thompson, Thompson, and Daily;[60] and Youmans[67]). Venous congestion has been shown to have a similar effect (Rowe,[54] Plass and Rourke,[50] and Reiss[51]).

It is not surprising, therefore, that attention has been directed by many observers to the increase in volume of an extremity when it is dependent or when the venous return is partly or entirely occluded (Atzler and Herbst,[5] Stead and Kunkel,[58] Wells,[65] Waterfield,[64] Mende,[44] White and Jones,[66] Drury and Jones.[26]) Mosso, using a delicate balancing board, found that when a subject assumed the horizontal position after standing for some time, the weight of the feet end of the board only slowly decreased, in spite of the fact that presumably the excess blood leaves the lower extremities almost immediately.

Figs. 2 and 3 show the brass chambers used to determine the leg and arm volumes, respectively. Each chamber is used in an identical manner. Several water outlets tap the chamber, and a manometer on the outside indicates the water volume at any level. For a determination, the extremity is dipped into the chamber until it touches the bottom. An adjustable step in the leg chamber facilitates its use for individuals with shorter legs. With the extremity in place, water is run in until it overflows the desired outlet, the outlets below being clamped. The extremity is then removed and the volume difference is noted on the manometer, indicating the volume of the extremity.

Determinations were made of the difference in volume of the lower extremities of fourteen volunteer interns upon arising in the morning and retiring at night. The volumes were determined immediately upon arising and just before retiring.

In six cases of inflammation of the extremities, the decrease in tissue tension was compared with the decrease in volume after elevation.

In seventeen cases of inflammation of an extremity, the increased volume of the affected member over that of the opposite normal extremity was determined, except in a few cases where an estimation of the volume was made by measuring the circumference.

Skin Surface Temperatures in Inflammation

In thirty-five cases of inflammation of the extremities, the skin surface temperatures of the normal and affected extremity in each case were determined. In many cases, volumes of the extremities and tissue tensions were also determined.

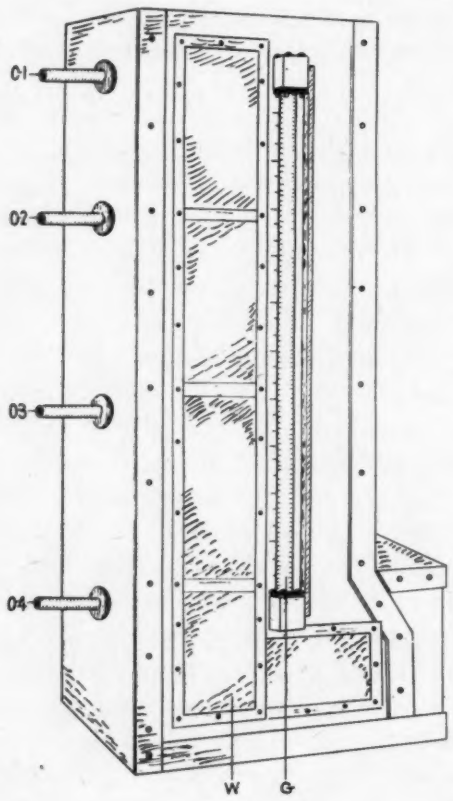


Fig. 2.—Brass chamber for measuring volume of lower extremity.

Protein Content of Serous Exudate in Human Inflammations

In ten cases of inflammations of the extremities, the specific gravity of the subcutaneous edema fluid was determined (Bellis[8]), and the protein content calculated as serum.

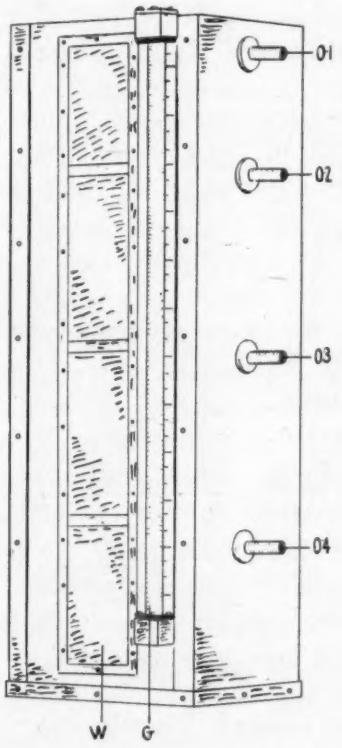
Inflammation in the Experimental Animal

For the purpose of experimentally induced inflammation, rabbits were used in most cases, the animal being anesthetized and one ear or extremity held in water at 60° C. for thirty seconds. In twelve hours this

gives an edematous extremity with most of the characteristics of human inflammation.

In five animals the affected extremity was placed in an air plethysmograph and the volume changes noted. In addition, the blister fluid was analyzed for protein and nonprotein nitrogen.

In four animals the edema fluid protein was compared with the plasma protein, the edema fluid pressure was determined, and the volumes of the extremities measured. Edema fluid was readily obtained, either by aspirating a blister or nicking the skin superficially and allowing it to flow out into a small test tube. Oxalate must be present to prevent coagulation, since the edema fluid contains so much protein that coagulation takes place quite readily.



W WINDOW
G GLASS TUBE GAGE
01, 02, 03, 04 WATER OUTLETS

Fig. 3.—Brass chamber for measuring volume of upper extremity.

To determine the efficiency of other irritants in producing inflammation, four piebald rats were injected subcutaneously with 0.1 c.c. of croton oil, 0.1 c.c. saturated sodium chloride solution, 0.1 c.c. half-saturated peptone solution, and 0.1 c.c. of mustard oil. Since equally

edematous areas were produced by each agent, some experiments were undertaken in rabbits. In one rabbit, 0.1 c.c. saturated sodium chloride solution and in another rabbit 0.1 c.c. half-saturated peptone solution was injected subcutaneously with no inflammation at the end of twenty-four hours sufficient for experiment.

Since croton oil seemed to have the desired inflammatory effect, inflammation was produced by this medium in three rabbits, the volumes of the inflamed ears and legs were determined, the edema fluid pressures determined, and the edema fluid protein compared with the plasma protein.

In four rabbits, complete physical studies were made. In each, the tarsosural region was depilated with barium sulfide and a sample of cardiac blood aspirated for control serum protein determination. The animal was then anesthetized and the depilated extremity immersed in water at 60° C. for one minute. Twenty-four hours later the serum protein was again determined and the animal reanesthetized. The tissue fluid pressure, its pH by the indicator method, and its protein content were determined. The pH of the blood plasma was similarly determined. Capillary pressures were obtained by intubation of capillaries in the inflammatory field. Finally, the volumes of the extremities were determined. The pH values were obtained because some investigators have cited significant changes in inflammation.

Any study of inflammation must, of necessity, consider the vacillating capillary pressure, the determination of which is delicate work. Capillaries in the living individual have been adequately described by many observers, but the determination of their intraluminal pressures has defied investigators until quite recently.

The blanching pressure and the pressure required to stop bleeding are inaccurate methods since they occasionally give values lower than venous pressure in the same individual. The figures so obtained are probably the pressures required to empty the subpapillary venous plexuses. The pressure necessary to prevent wheal formation also gives an abnormal reading. The slightest variations in the surroundings may lead to remarkable changes in the capillary diameter and its pressure; in fact, capillary pressures ranging from 1.5 to 71 mm. Hg have been recorded for the normal (Strax and deGraff[59]).

Using the method of Lombard[41] and Landis,[39] micropipettes can be drawn from fine glass tubes, and capillary cannulation accomplished with the Chambers[18] micromanipulator. The apparatus* is diagrammed in Fig. 4 as assembled for use. Essentially, it is composed of two units functioning independently or dependently. On the right is the pressure system. This consists of a reservoir of 0.3 per cent sodium citrate

*Loaned through the courtesy of Dr. George E. Fahr of the Minneapolis General Hospital.

in physiologic saline solution, adjusted to pH 7.3 with potassium acid phosphate solution communicating with a finely adjusted syringe, a mercury U manometer and the cannulating unit. The latter consists of fine flexible copper wire tubing attached by a rubber pressure tubing connector to a short length of heavy glass capillary tubing fixed in the jaws of the micromanipulator. In turn, by means of beeswax the heavy capillary tubing is fixed, end on, to the micropipette.

Although an electric heating apparatus is available for drawing the pipettes by a falling weight, better yields are obtained by drawing them by hand; that is, about one of every fifty meets the requirements. The diameter of the tip, examined under the microscope, should be between 8 and 15 μ in diameter and should be angled at 20 to 30°. A Spencer binocular dissecting microscope (magnification ×85; 12.5 ocular; objective ×6.8) in conjunction with a Spencer universal microscope lamp is

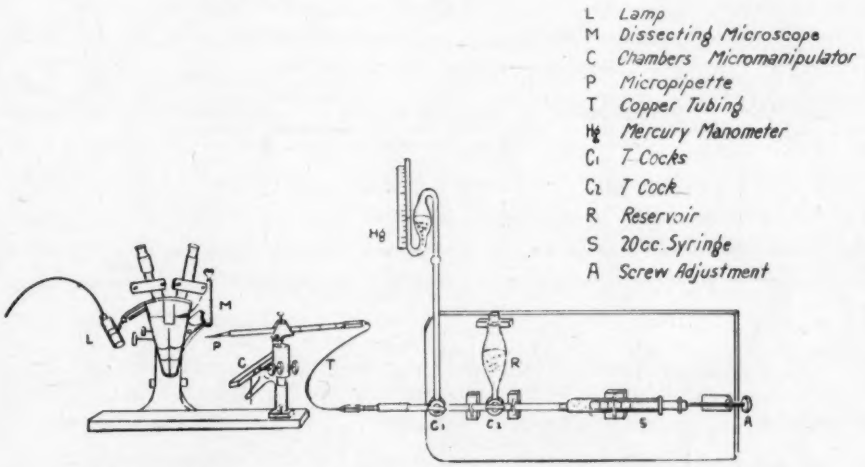


Fig. 4.—Apparatus for direct measurement of capillary pressure.

used. The pipette must be dust free, or else the fine tip will be plugged with dust granules. Therefore, a considerable quantity of citrate solution is used to flush the tip, the flushing process being observed through the microscope. The skin to be penetrated is steadied by sandbags and covered with a thin film of glycerin to avoid multiple reflections, and the microscope lamp is so angled that the reflection is not passed to the observer.

Using the Chambers micromanipulator, the pipette is passed through the skin, maintaining about 2 mm. Hg positive pressure. Immediately, the capillary seen a moment before as a curling string of corpuscles with a steady flow at one end and a pulsatile flow at the other end, disappears from view. This is due to a clamping shut of the little vessels, probably reflex. The observer then waits for three or four minutes, following which the capillary reopens. The pipette is then brought closer and

TABLE I

EFFECT ON SYSTOLIC BLOOD PRESSURE (MM. HG) OF POSITIONING ARM

NO.	HORIZONTAL (H)	ELEVATED (E)	DEPENDENT (D)	DIFFERENCES		
				E-H	H-D	E-D
1	96	80	130	16	34	50
2	106	90	120	16	20	36
3	120	92	132	28	12	40
4	106	94	116	12	10	22
5	108	90	114	18	6	24
6	120	98	132	22	12	34
7	110	76	116	34	6	40
8	88	68	110	20	22	42
9	108	66	116	42	8	50
10	124	80	150	44	26	70
11	120	76	148	44	28	72
12	110	76	128	34	18	52
Average				27	17	44

TABLE II

EFFECT OF ELEVATION ON SKIN SURFACE TEMPERATURES OF FINGERS (° C.)

NO.	HORIZONTAL	ELEVATED	TEMPERATURE DIFFERENCE
1	29.3	25.5	3.8
2	30.0	26.0	4.0
3	27.4	24.0	3.4
4	30.4	24.2	6.2
5	32.5	27.6	4.9
Average			4.4

TABLE III

SKIN SURFACE TEMPERATURES (° C.) BEFORE AND AFTER ELEVATION OF RIGHT LOWER EXTREMITY FOR TWELVE HOURS

REGION	BEFORE ELEVATING THE RIGHT LEG		AFTER ELEVATING THE RIGHT LEG	
	RIGHT	LEFT	RIGHT	LEFT
Upper thigh	33.7	33.7	32.5	32.3
Lower thigh	33.1	32.9	32.3	32.5
Upper tibia	33.5	33.1	29.3	32.1
Ankle	34.5	34.3	29.3	33.1
Dorsum foot	33.7	33.7	27.1	33.7

TABLE IV

EFFECT OF TWELVE HOURS' SEMI-FOWLER'S POSITION ON SKIN SURFACE TEMPERATURES OF LOWER EXTREMITIES (° C.)

REGION	BEFORE	AFTER
Upper thigh	32.0	32.2
Lower thigh	31.0	32.0
Upper tibia	29.8	31.0
Middle tibia	31.0	31.6
Ankle	29.6	30.4
Dorsum foot	27.4	29.2
Base great toe	26.0	29.4
Medial great toe	22.2	23.4

Increase in volume = 350 c.c.

directed toward the mid-portion of the capillary, and, if possible, opposite to the direction of the stream. Entrance into the vessel is evident when a stream of corpuscles travels up the pipette. Gradual pressure is then made by means of the syringe until the corpuscles pulsate but do not move. The pressure is then read on the mercury manometer.

Capillary intubation in the anesthetized rabbit is especially difficult. The rapid, jerky respirations not only make it difficult to focus the capillary but tax the patience of the operator in his efforts to pierce the jerking vessel. In fact, penetration must be accomplished in an interval between respirations. Fracturing of the cannula tip, making its discard necessary, is often a discouraging result of the respiratory jerking of the leg.

The animals were anesthetized with intravenous pentobarbital sodium, and no information is available as to the effect of the anesthetic itself on the capillary pressure.

In order to study the flow in the lymphatics from inflamed areas, three dogs were used. Each animal was anesthetized with intraperitoneal pentobarbital sodium (35 mg. per kilogram). In one, the skin of the front of the foreleg and back of the hindleg was incised and retracted and 2 c.c. of 2 per cent aqueous trypan blue injected into each foot pad. Light passive motion of the foot immediately brought the lymphatics into view as blue streams of a more purple color than the veins. Using a hand lens, a large lymphatic trunk was cannulated with a fine glass cannula. With an assistant counting the number of drops falling, the flow was determined after massage and passive motion, and, finally, after immersing the paw in a beaker of water at 60° C. for one minute. An identical procedure was done in a second animal except that the heating temperature was 45° C. In the third dog, lymph flow was determined without heating the paw.

RESULTS

Position and Blood Flow in the Patient

Arterial Blood Pressure.—The average radial systolic blood pressure in twelve individuals was 27 mm. Hg higher with the extremity in the horizontal position than in the elevated position, and 44 mm. Hg higher with the extremity dependent than in the elevated position. An average increase of 17 mm. Hg took place when the extremity was brought from the horizontal to the dependent position (Table I).

Skin Surface Temperatures.—In five normal individuals, the average skin surface temperature of the finger tip was 4.4° C. lower than at horizontal position after elevating the extremity perpendicular to the horizontal trunk for an hour (Table II).

In six individuals, the temperatures in the foot and toes were depressed from 2 to 5° after elevation at 60° with the horizontal position for twelve hours (Table III is a typical case).

After twelve hours in the semi-Fowler's position, the skin surface temperatures of the lower extremity were found to increase as much as 3.4° C. and the volume of the extremity to increase 350 c.c. Control readings were previously obtained in the horizontal position (Table IV).

Tissue Tensions in the Patient

Normal Tissue Tension.—In 103 routine outpatients, the subcutaneous tissue tension on the dorsum of the hand averaged 1.8 mm. Hg (mean 2.2 mm. Hg), and the tension on the dorsum of the thigh averaged 2.5 mm. Hg (mean 2.7 mm. Hg) (Table V).

TABLE V

NORMAL SUBCUTANEOUS PRESSURES (RESISTANCE TO DISTENTION) IN 103 AMBULANT PATIENTS (MM. HG)

DORSUM HAND		MID-THIGH	
NUMBER OF PATIENTS	PRESSURE	NUMBER OF PATIENTS	PRESSURE
11	0	3	0
42	1	20	1
23	2	34	2
13	3	22	3
8	4	18	4
5	5	6	5
1	6		
Average	1.8		2.5
Mean	2.2		2.7

In twenty-eight ambulatory patients, the intramuscular tension at rest averaged 3 to 7 mm. Hg higher than in twenty-six patients undergoing bed rest (Table VI).

TABLE VI

NORMAL INTRAMUSCULAR PRESSURES (MM. HG)

	NO. CASES	REGION	AV. PR.	RANGE
Tensions in ambulatory patients	16	Deltoid	4-5	2-8
	10	Quadriceps femoris	3-4	1-6
	2	Tibialis anterior	7	6-8
Tensions after several days of bed rest	2	Biceps brachii	0	0
	14	Deltoid	0+	0-3
	10	Quadriceps femoris	0-1	0-4

Tissue Tension in Inflammation.—In acute fractures, the average tissue pressures ranged from 8 to 16 mm. Hg, compared with the average 0 to 9 mm. Hg for the uninjured side. After immobilization, the average tissue pressures on the injured side were 0 to 12 mm. Hg, compared with 0 to 14 mm. Hg for the uninjured side (Table VII).

In a series of miscellaneous inflammations, the subcutaneous tissue pressure averaged 4 to 20 mm. Hg, compared with 0 to 4 mm. Hg on the uninjured side. In five cases of cardiac decompensation the subcutaneous tissue pressures ranged from 13 to 22 mm. Hg (Table VIII).

TABLE VII

TISSUE TENSIONS BEFORE AND AFTER IMMOBILIZATION OF FRACTURES (TENSIONS IN MM. HG)

ACUTE FRACTURES	BEFORE IMMOBILIZATION					AFTER PARTIAL IMMOBILIZATION				
	AV., INJURED SIDE	RANGE	AV., UNINJURED SIDE	RANGE	NUMBER OF CASES	AV., INJURED SIDE	RANGE	AV., UNINJURED SIDE	RANGE	NUMBER OF CASES
1. Humerus										
a. intramuscular	15-16	6-28	5	0-12	7	5-6	2-12	2	0-6	3
b. subcutaneous	13	3-36	1-2	0-4	6	0-1	0-3	0-1	0-3	5
2. Forearm										
a. subcutaneous	16	16-16	6	4-8	2	2	0-4	2	2-2	2
3. Shaft femur										
a. intramuscular	14	14	6	6	1	2	2	2	2	1
4. Knee										
a. intramuscular	20	20	6	20	1	----	----	----	----	----
b. subcutaneous	16	10-22	5	0-10	2	----	----	----	----	----
5. Leg										
a. intramuscular	18	12-26	8-9	8-10	3	----	----	----	----	----
b. subcutaneous	15	6-24	0	0-0	2	6	0-12	1	0-2	2
6. Ankle										
a. subcutaneous	10	10	0	0	1	----	----	----	----	----
7. Clavicle										
a. subcutaneous	8	8	0	0	1	----	----	----	----	----
FRACTURES AFTER PARTIAL IMMOBILIZATION										
1. Humerus	----	----	----	----	----	4	4	8	8	1
2. Forearm	----	----	----	----	----	2	2	14	14	1
3. Femur	----	----	----	----	----	1-2	0-4	7-8	6-12	4
4. Knee	----	----	----	----	----	0	0-0	6	2-10	2
5. Leg	----	----	----	----	----	0	0	6	6	1

TABLE VIII

TISSUE PRESSURES IN MISCELLANEOUS AFFECTIONS (MM. HG)

AFFECTION	BEFORE IMMOBILIZATION					AFTER IMMOBILIZATION				
	AV., INJURED SIDE	RANGE	AV., UNINJURED SIDE	RANGE	NUMBER OF CASES	AV., INJURED SIDE	RANGE	AV., UNINJURED SIDE	RANGE	NUMBER OF CASES
A. Arthrodeses of shoulder (all intramuscular)	----	----	----	----	----	6	4-8	17	16-18	2
B. Acute shoulder dislocations (subcutaneous)	4	4	0	0	1	----	----	----	----	----
C. Infections of extremities										
1. Skin elbow (subcutaneous)	20	20	3	3	1	----	----	----	----	----
2. Finger (subcutaneous)	16	16	4	4	1	----	----	----	----	----
3. Knee (quadriceps femoris)	----	----	----	----	----	0	0	4	4	1
4. Osteomyelitis leg (intramuscular)	----	----	----	----	----	0	0	5	5	1
D. Infection of buttock (subcutaneous)	12	----	0	----	1	----	----	----	----	----
E. Residual poliomyelitis (intramuscular)										
1. Deltoid	----	----	----	----	----	0	0-0	6	2-8	2
2. Quadriceps fem.	----	----	----	----	----	2	2	4	4	1
3. Tibialis anter.	----	----	----	----	----	0	0	4	4	1
F. Cardiac decompensation										1
1. Tibialis anterior										
a. Intramuscular	21-22	14-30	(before medical		2	0	0	(after medical		
b. Subcutaneous	12-13	8-14	treatment)		3			treatment)		
G. Hemangioendothelioma of shoulder girdle										
a. shoulder girdle	50	----	0							
b. pronator teres	30	----	4							
c. dorsum hand	23	----	0							

In a series of twenty cases of inflammation of the extremity in which the skin surface temperatures were also determined, the tissue tensions on the affected sides were always higher than on the normal. In one case, a subcutaneous pressure of 56 mm. H_2O was observed (Table IX).

TABLE IX

MAXIMUM INCREASES IN SKIN SURFACE TEMPERATURE (° C.), TISSUE TENSION (CM. H_2O), VOLUME (C.C.), AND CIRCUMFERENCE (CM.) OF INFLAMED EXTREMITIES, ABOVE CORRESPONDING NORMAL EXTREMITY (35 CASES)

CASE NO.	MAXIMUM TEMPERATURE INCREASE	MAXIMUM TISSUE TENSION INCREASE	MAXIMUM VOLUME INCREASE	MAXIMUM CIRCUMFERENCE INCREASE
1	2.4	---	---	---
2	3.9	---	---	---
3	2.8	---	---	---
4	3.0	---	---	---
5	3.2	---	---	---
6	3.2	---	---	---
7	7.2	---	---	---
8	3.6	---	---	---
9	1.4	---	---	---
10	2.4	---	---	---
11	3.2	---	---	---
12	4.4	---	---	---
13	2.6	---	---	---
14	5.8	---	---	---
15	5.4	---	---	---
16	3.0	---	---	---
17	0.8	10.0	---	---
18	1.8	2.6	---	---
19	1.2	18.0	1000	---
20	1.4	7.0	200	---
21	0.6	10.0	1650	---
22	1.7	5.0	500	---
23	1.4	27.0	2900	---
24	2.0	44.0	4150	---
25	1.0	22.0	1150	---
26	0.8	24.0	1500	---
27	1.4	8.0	900	---
28	1.6	26.0	4500	---
29	1.2	13.0	850	---
30	3.4	11.0	800	---
31	1.4	10.0	---	6.5
32	3.8	13.0	---	9.0
33	0.6	12.0	---	5.0
34	2.0	1.0	---	5.0
35	0.6	4.0	---	7.0

Position and Volume Changes in the Human Being

In fourteen interns the increases in volume of the lower extremity at night over that in the morning ranged from 50 c.c. to 800 c.c. Expressed as increase per 100 c.c. of extremity, the increases ranged from 0.5 c.c. per 100 c.c. to 7.3 c.c. per 100 c.c. These increases amounted to 2 to 7 per cent of the leg volume (Table X).

In six cases of infection of the upper or lower extremity, the volume decreases after elevation ranged from 365 c.c. to 1,647 c.c. (Table XI).

In infections of the lower extremity, as great an increase in volume as 4,500 c.c. was observed over that in the corresponding normal extremity (Table IX).

Skin Surface Temperatures in Human Inflammation

In thirty-five cases of inflammations of the upper or lower extremities, there were increases of skin temperature up to 7° C. on the affected side (Table IX).

TABLE X

DIFFERENCE IN VOLUME OF ONE LOWER EXTREMITY IN 14 HEALTHY YOUNG MEN BETWEEN ARISING IN MORNING AND RETIRING AT NIGHT

CASE	INITIAL LEG VOLUME	INCREASE (C.C.)	INCREASE PER 100 C.C. OF EXTREMITY
1	9250	50	0.5
2	10250	600	6.0
3	9000	300	3.3
4	11150	550	5.0
5	11250	100	1.0
6	9950	500	5.0
7	13050	650	5.0
8	10900	800	7.3
9	8650	200	2.3
10	10150	300	2.0
11	9750	250	2.5
12	10200	500	5.0
13	11550	550	5.0
14	10750	350	3.0

TABLE XI

TISSUE TENSION AND VOLUME CHANGES OF INFLAMED EXTREMITIES ATTENDING ELEVATION

CASE	AREA INVOLVED	TISSUE TENSION (MM. HG)		VOLUME DECREASE (C.C.)	TIME INTERVAL
		1	2		
1	Furuncle, elbow	12	4	447	15 days
2	Thrombophlebitis, leg	20	8	870	12 hours
3	Thrombophlebitis, leg	40	4	365	14 days
4	Phlebitis, arm	--	--	415	4 hours
5	Thrombophlebitis, leg	10	2	988	4 days
6	Cellulitis, leg	--	--	1647	17 days

Protein Content of Serous Exudates in Human Inflammation

In ten cases of inflammation of the extremities, the specific gravity of the edema fluid was found to range from 1.019 to 1.030, corresponding to protein contents of 4.1 to 7.9 per cent, calculated as serum (Table XII).

Correlation of Physical Factors in Experimental Inflammation

Capillary Pressures, Tissue Tensions, Tissue Fluid Protein, Plasma Protein, pH of Tissue Fluid, Volume Changes.—In four rabbits and one cat, heat inflammation caused increases in volume ranging from 5 to 10 c.c. distal to the tarsosural joint, as measured in the air plethysmograph.

TABLE XII

SPECIFIC GRAVITIES OF SUBCUTANEOUS EDEMA FLUIDS IN INFLAMMATIONS OF THE EXTREMITIES

CASE	SPECIFIC GRAVITY	PROTEIN (GM. PER 100 C.C.) AS SERUM
1	1.028	7.2
2	1.026	6.5
3	1.024	5.8
4	1.025	6.2
5	1.018	3.7
6	1.019	4.1
7	1.025	6.2
8	1.028	7.2
9	1.030	7.9
10	1.026	6.5

The blister fluid protein content ranged from 4.6 to 6.3 per cent and the nonprotein nitrogen content from 48 to 126 mg. per cent (Table XIII, a, b, c, d, and e).

In four other rabbits inflammations of the ear by heat caused volume increases ranging from 11 to 25 c.c. In the heat inflammations of the leg, the volume increases ranged from 109 to 60 c.c. The edema fluid protein levels ranged from 3.9 to 4.7 per cent, which were about equal to the plasma protein levels. The tissue pressures in the involved side ranged from 12 to 28 mm. Hg (Table XIII, f, g, h, and i).

TABLE XIII

EFFECT OF EXPERIMENTAL INFLAMMATION ON VOLUME CHANGE, PLASMA PROTEIN, TISSUE FLUID PROTEIN, AND TISSUE PRESSURE

	CASE	PLASMA PROTEIN (GM. PER 100 C.C.)		EDEMA FLUID		VOLUME INCREASE (C.C.)	TISSUE TENSION (MM. HG)	TIME INTERVAL (HOURS)
		PREOPERATIVE	POSTOPERATIVE	PROTEIN (GM. PER 100 C.C.)	N.P.N. (MG. PER 100 C.C.)			
Heat Inflammation	a (Cat)	--	--	--	--	9.5	--	2.5
	b	--	--	5.2 5.4	48.2	12.5	--	6
	c	--	--	4.6	70.6	5	--	2
	d	--	--	6.3	126	6	--	4
	e	--	--	5.2 5.8	79 84	17	--	14
	f	--	4.6	4.6 4.7	--	60	28	8
	g	4.9 4.7	4.1 4.7	3.9 4.1	-- --	35 25 (Ear)	22	6
	h	4.5	3.3 3.5	4.4 4.5	--	10	18	24
	i	5.4	5.2	4.0	--	25 11 (Ear)	12	36
Croton Oil Inflammation	j	--	2.5	2.2	--	--	28	24
	k	4.6	3.6	3.3 3.5	--	45 15 (Ear)	16	24
	l	6.3 6.2	5.0 5.3	4.6 4.7	--	--	28	24

In three rabbits with ear and leg inflammations by croton oil, the ear volume in one increased 15 c.c. and the leg volume 45 c.c. The edema fluid proteins at the same time ranged from 2.2 to 4.7 per cent and the plasma proteins from 2.5 to 5.3 per cent (Table XIII, j, k, and l). Preoperative plasma protein levels ranged from 4.5 to 6.3 per cent. In two rabbits the tissue tensions in the inflamed area were 28 and 16 mm. Hg, respectively. Control tissue tensions in this series were 0 to 2 mm. Hg.

In four rabbits in which heat inflammation of the leg was produced, the serum protein was found to be lowered and the edema fluid protein levels ranged from 2.8 to 4.1 per cent. Capillary pressures ranged from 31 to 40 mm. Hg in the inflamed area, while the extremities increased in volume, ranging from 10 to 65 c.c. In three of these animals, simultaneous determinations of plasma and edema fluid pH showed no practical differences (Table XIV).

TABLE XIV

EFFECT OF EXPERIMENTAL HEAT INFLAMMATION IN RABBIT EXTREMITY ON FACTORS WHICH REGULATE FLUID INTERCHANGE

CASE	PLASMA PROTEIN (GM. PER 100 C.C.)		EDEMA FLUID (GM. PER 100 C.C.)		TISSUE TENSION (MM. HG)	CAPILLARY PRESSURE (MM. HG)	VOLUME INCREASE (C.C.)
	PRE-OPERATIVE	POST-OPERATIVE	PROTEIN	PH			
a	6.4	6.0	4.1	--	31	40	24
b	4.5	3.8 (pH 7.6)	2.8	7.4	20 (Control = 0)	31	10
c	4.6	4.3 (pH 7.5)	3.1	7.4	16 (Control = 0)	33	55
d	4.0	3.5 (pH 7.5)	3.1	7.5	26 (Control = 4)	27	65

Lymph Flow.—The lymph flow through the cannulated lymphatic of the dog's leg is practically zero at rest, but is increased by massage or passive motion. In one of the three animals studied, heating the extremity to 45° C. caused the lymph to flow out of the cannula in a steady stream (Table XV).

TABLE XV

EFFECT OF HEAT INFLAMMATION ON LYMPH FLOW IN EXTREMITY OF DOG

NO.	FLOW DURING INACTIVITY	VOLUME FLOW AFTER MASSAGE OR MOTION	TISSUE TENSION (MM. HG)
1	0 in 3 min.	(a) 3 c.c. in 3 min.	--
		(b) 0 in 2 min. after heating at 60° C.	--
2*	0 in 2 min.	.25 c.c. in 1 min. (clotting of lymph in cannula)	11
3	0 in 3 min.	(a) 2.0 c.c. in 3 min.	--
		(b) 4 to 5 c.c. per min. after heating to 45° C.	--

*Twenty-four hours after inflammation.

CLINICAL APPLICATIONS

Infections of the Extremities

Types of Casts.—Hilton[36] wrote a fascinating and informative treatise on rest and pain in which he stressed the importance of rest in the treatment of infections. Those skilled in the treatment of tuberculosis will attest to this fact. A short time later Dennis[24] pointed out the great value of immobilization in plaster in the treatment of compound fractures, and Orr[48] adopted rigid immobilization in plaster as a constant sequel to sequestrectomy for chronic osteomyelitis, shortly thereafter employing closed plaster casts and massive vaseline packs together with extensive osteotomy in acute osteomyelitis.

In the surgical clinic of the University of Minnesota Hospitals, the essential treatment of acute infections of the extremities has been (a) rest by immobilization of the entire extremity involved in a plaster cast including the trunk, and (b) elevation by positioning the affected member in the cast in such a manner as to most rapidly drain the edema fluid toward the heart by gravity. Fig. 5 shows the type of shoulder spica applied in the event of infection involving the upper extremity. With the arm in midelevation the extremity is above heart level when the patient is standing, sitting, or lying.

Fig. 5.—Type of shoulder spica applied for inflammation of upper extremity.

Appropriate windows are cut in the cast to permit frequent observation of the infected area; when there is definite evidence of suppuration, not before, a small incision is made for evacuation of the exudate through the cast window. Large incisions have no additional advantage, producing only more trauma to tax the patient's already burdened healing powers.

In acute osteomyelitis of the tibia, for example, a body plaster is applied extending from the waist to the toes on the affected side, the affected member being placed in elevation (Fig. 6). A window is cut in the plaster directly over the tender area permitting incision when evidence of abscess formation is present. The only type of case in which early incision is warranted is acute tenosynovitis. In such cases, the necessity of early opening of the tendon sheath to preserve the nutrition and identity of the tendon has been pointed out by Kanavel.[37]

The immobilization which can be secured by a body cast is ever so much more efficient than that obtained by any other method. Sandbags, traction, voluntary rest, and other measures do not begin to afford the relaxation and rest to an inflamed extremity that an adequate plaster cast will. A patient with an infected knee joint, treated with adequate traction, may cry with pain when the bed is touched. After the application of a cast the patient can be turned over in bed without causing him the slightest discomfort.

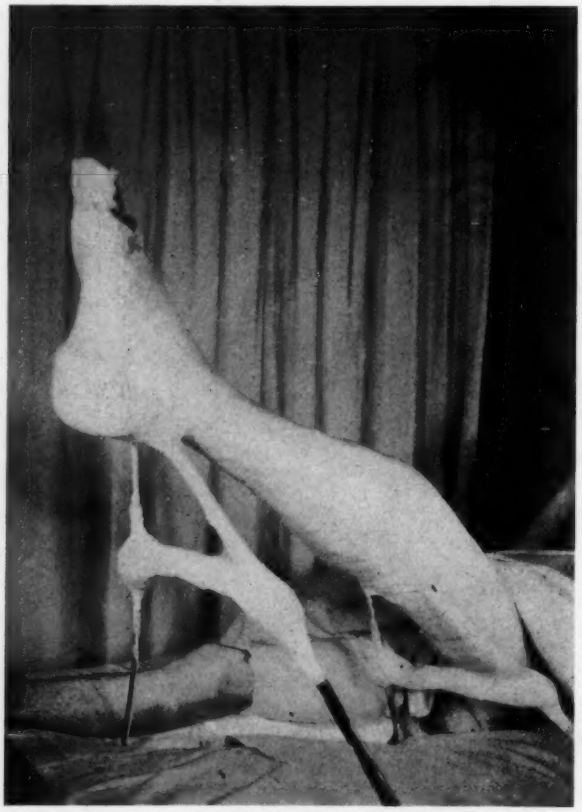


Fig. 6.—Type of hip spica cast applied for inflammation of the lower extremity.

Results of Immobilization and Elevation.—A questionnaire was mailed to all patients hospitalized in the University of Minnesota Hospitals in the six-year period from January, 1934, to December, 1939, for infections of extremities and who were treated by immobilization in plaster

casts. In the letter, the patient was asked to describe his present condition or to return to the outpatient clinic for examination. The total number of cases finally available for tabulation was 116 (Table XVIa). Forty-one, or 35.3 per cent, returned for examination; forty-nine, or 42.2 per cent, replied by mail; eighty-three, or 19.8 per cent, did not reply but were recently examined in the outpatient clinic; and three, or 2.5 per cent, were dead.

TABLE XVI

CLASSIFICATION OF 116 PATIENTS TREATED BY IMMOBILIZATION IN PLASTER CASTS FOR INFLAMMATION OF THE EXTREMITIES

	NO.	PER CENT
a. Results of mailing questionnaires:		
Patients returning for examination	41	35.3
Additional replies	49	42.2
Those not replying but recently examined	23	19.8
Deaths	3	2.5
Total number of patients in study	116	100.0
b. Classification of inflammations included in this study:		
Hand and forearm	25	21.5
Lower extremity	8	6.9
Osteomyelitis:		
acute	12	10.3
chronic	56	48.3
Primary septic arthritis	15	13.0
Total	116	100.0

It was found (Table XVIb) that twenty-five cases, or 21.5 per cent, were infections of the hand or forearm; eight, or 6.9 per cent, were lower extremity infections; twelve, or 10.3 per cent, were acute osteomyelitis; fifty-six, or 48.3 per cent, were chronic osteomyelitis; and fifteen, or 13.0 per cent, were primary septic arthritis.

Good results, that is rapid control of the infection with healing, were obtained in 72.2 per cent; fair results, that is control of the infection with delay or recurrence, were obtained in 21.6 per cent; poor results, that is uncontrolled infections, were obtained in 6.0 per cent. These results are itemized in Table XVII. Itemization of the patients in each pathologic classification is recorded in Table XVIII.

TABLE XVII

SUMMARIZED RESULTS OF TREATMENT OF INFLAMMATIONS OF EXTREMITIES BY IMMOBILIZATION AND ELEVATION IN PLASTER CASTS

TYPE OF INFECTION	GOOD (RAPID CONTROL WITH HEALING)		FAIR (CONTROL WITH DELAY OR RECURRENCE)		POOR (INFECTION NOT CONTROLLED)	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Hand and forearm	20	80	3	12.0	2	8
Lower extremity	7	87.5	1	12.5	0	0
Septic arthritis	10	66.6	4	26.6	1	6.6
Osteomyelitis:						
acute	8	66.6	3	25.0	1	8.3
chronic	34	60.7	18	32.1	4	7.2
Totals	79	72.2	29	21.6	8	6.0

TABLE XVIII

DETAILED RESULTS IN TREATMENT OF INFECTIONS BY IMMOBILIZATION IN PLASTER

	TYPE	NO.	TREATMENT	DAYS IN CAST (AV.)	DAYS IN HOSPITAL (AV.)	RESULT
Hand and forearm infections	Traumatic	8	Shoulder spica	26	20	3 Good 3 Ankylosis 2 Finger amputated
	Fascial space	6	Shoulder spica	11	15	3 Excellent 2 Stiff or ankylosed 1 Amputation of digit advised
	Lymphadenitis	1	Shoulder spica	6	14	1 Excellent
	Tenosynovitis	1	Shoulder spica	20	40	Ankylosis
	Soft tissue infection with bone involvement	4	Shoulder spica	25	50	3 Healed with ankylosis 1 Amputation through carpus
	Furuncle	1	Arm cast, suspended	5	7	Death; septicemia and lung abscess
	Forearm	4	Shoulder spica	10	16	3 Excellent 1 Stiff elbow
Lower extremity infections	Cellulitis	4	Hip spica, long leg	12	14	3 Good 1 Ankylosis
	Gunshot	1	Hip spica	180	135	Draining; crutches
	Puncture (manure fork)	1	Hip spica	25	40	Excellent
	Infected varicose ulcer	1	Long leg	30	35	Good
Primary septic arthritis	Multiple	2	Spica	92	240	Ankylosis or limitation
	Sacroiliac and hip	3	Hip spica	80	68	Ankylosis in all
	Knee	6	Hip spica or long leg	39	25	4 Ankylosis 2 Good function; both children aged 2 yrs.
	Ankle	2	Long leg Short leg	13 2 yrs.	14	1 Excellent 1 Ankylosis; good function
	Elbow	1	Arm cast suspended	10	48	Ankylosis
	Hip, traumatic	1	Spica	5	7	Death
Acute osteomyelitis	Tibia or fibula	4	Hip spica; long and short leg casts	84	54	Good in all
	Femur	3	Hip spica	57	45	2 Good 1 Death; pneumonia
	Radius or ulna	2	Shoulder spica; arm suspended	26	11	1 Good 1 Ankylosis of elbow
	Sacroiliac	2	Body cast	62	22	Good
	Scapula	1	Airplane	--	40	Good
Chronic osteomyelitis	56 cases; average duration 8.4 yrs. when first seen		Casts	190	83	34 Good (16 observed more than 2 yrs.) 18 Recurrences 4 Amputations 2 Fair 18 Ankylosis

DISCUSSION

Effect of Immobilization

Although it has been suggested that immobilization causes atrophy, the actual evidence of any great degree of atrophy is lacking. The work of Sherrington and others has adequately demonstrated the proprioceptive nature of muscle tone, a phenomenon which can be initiated by such actions as passive changes in the position of the head. Some experimenters have observed minimal atrophy in the extremities of animals encased in plaster casts, but they offer evidence that such minimal atrophy is temporary and may be almost obviated by properly applied casts. It cannot be proved that normal muscles, immobilized in casts, are in a state of inactivity; rather, muscle tone is preserved and normal voluntary motion, although partly isometric, begins with the disappearance of pain.

Inflammation and Pain.—Inflammation is in large part a reflex act initiated by pain (Odermatt,[46] Rosenbach,[53] Ricker and Regendanz[52]). Spiess[56] emphasized that anesthetized wounds undergo less inflammation, and he stated that there is a direct relationship between anesthesia and healing. He noted that the more painful a wound is the more it becomes inflamed. If the pain is removed by means of a local anesthetic, the inflammation diminishes to an extraordinary degree.

Bruce[14] showed experimentally that conjunctival anesthetics prevented inflammation, that the initial vasodilation in inflammation was an axon reflex, and that the development of edema is dependent upon the intactness of the axon reflex. In his experiments he used alypin, a local anesthetic, to prevent mustard oil inflammation in the eye. Bardy[6] advocated the use of morphine to reduce inflammation and stated that *dolor* was responsible for *turgor, rubor,* and *calor.*

Inflammation and Rest.—Since the lymphatic channels through which infections spread lie in the fascias overlying the muscles, lessening of muscle movement which accompanies immobilization in plaster serves to minimize dissipation of the infection, and must be an important factor in aiding the natural defenses of the body in localizing the infection. Experimentally, Beecher[7] has demonstrated the marked lymph flow attending muscular activity.

Adler,[3] speaking of tissue fluid, wrote, "The fluid spreads with more or less ease from one lymph space to another, the propelling forces being diffusion and mechanical pressure. The latter is caused, first, by contracting the muscles surrounding the lymph spaces, and second, by gravity and external mechanical pressure (massage)." The excellent work of McMaster, Hudack, and Parsons[43] illustrates the readiness with which the gentlest massage increases lymph flow.

Effect of Elevation

Elevation of an inflamed part diminishes the edema and increased venous pressure and reduces the temperature of the inflamed part. Because of the abnormal permeability, edema can be only diminished, since the capillary wall is then much more permeable to protein which escapes into the tissue spaces. Owing to the diminished transudation of fluid it effects, and the introduction of the effect of gravity on blood flow and on the edema fluid forming and already formed, elevation definitely reduces the tissue tension and volume of the extremity. Friedrich[31] taught that the rising tissue pressure compressed capillaries and caused gangrene.

Thus, the Fowler's position would be indicated for infections of the head and neck, and the Trendelenburg position in pararectal, scrotal, pelvic, and lower abdominal inflammations. Carrier and Rehberg[17] and Turner[61] showed that when the hand is above the base of the heart, capillary pressure is low, and when dropped below, the increase of capillary pressure is almost identical with the theoretic increment due to the hydrostatic pressure of the column of the venous blood.

Relation Between Capillary Pressure, Plasma Oncotic Pressure, Tissue Tension, and Tissue Oncotic Pressure.—Graham,[33] who first used the term colloid, mentioned that plasma colloids might exert an osmotic pressure in the blood. After Starling's demonstration[57] of the colloid osmotic pressure exerted by the plasma proteins, Schade and his coworkers[55] showed that in inflammation, especially in suppuration, the osmotic pressure of the tissue fluid may be as high as eleven atmospheres, and, therefore, inflammatory edema was merely an entire osmotic phenomenon. He gave proper importance, however, to the tissue tension, but Burch and Sodeman[15] showed that the tissue in developing edema was unusually high due to the tone of the connective tissue.

Landis[39] has shown that the blood pressure at the arteriolar end of the capillary loop is about 45 cm. water, that at the venous end is 22 cm. water, and that the colloid osmotic pressure of the blood is 36 cm. water. Thus, there is a tendency for ultrafiltration at the arterial end and a tendency to reabsorption of fluid at the venous end of the loop. That this ideal system operates only under "normal" conditions is well accepted. In inflammation or venous engorgement there is outpouring of filtrate into the tissue spaces. Some investigators have even assumed a linear relationship between rate of edema formation and difference between capillary pressure and the osmotic pressure of the plasma proteins.

The factors influencing the local formation of edema have been subjected to the most rigid investigations by competent observers, and it appears that the primary factors are (1) elevated capillary pressure, (2) lowered colloid osmotic pressure of the blood plasma, (3) damage to

the capillary wall, and (4) lymphatic obstruction. Contributory factors are (5) low tissue pressure, and (6) warmth. Krogh laid great stress on the intracapillary pressure, while Schade believed that the two most important balancing factors are the tissue tension ("Gewebsspannung") and the imbibition pressure of the interstitial colloids ("extracelluläre wasserdurchtränkte Bindegewebskolloid").

Drinker and Field[25] observed that edema fluid may contain as much as 4.5 per cent protein, and I have found blister fluid in experimentally produced burns to contain as much as 6 per cent protein, which would amount to 40 cm. water colloid osmotic pressure. Therefore, the tissue fluid may raise the osmotic pressure on the outside of the capillary to such a level that reabsorption of fluid by the capillary through osmotic means may be greatly slowed or even stopped. Specific gravity values for edema fluid corresponding to those I obtained have been found by Schade and others.

The subcutaneous pressures which were obtained in normal individuals correspond to the few recorded in the literature (Wells[65]). The tensions found in inflammations were always higher than normal, tending to limit capillary filtration (Beecher[7]). In addition, it may be observed that the tissue tensions in the normal extremities of individuals with immobilized infected extremities are higher than the average "normal." This is probably due to the double duty required of the remaining mobile extremity.

Fahr[27] has also stated that the sum of serum protein osmotic pressure and tissue tension need not equal the sum of edema fluid osmotic pressure and intracapillary pressure except in a state of equilibrium. If fluid is leaving the capillary, the hydrostatic capillary pressure will be so high that the sum of capillary pressure and edema fluid osmotic pressure will be greater than the first sum.

In our experiments (Table XIV), it may be seen that an equilibrium exists between the forces "pulling" water into the capillary and those "pulling" water into the tissues. For example, in terms of millimeters of mercury, in animal a:

Force pulling water into blood:
18 (6% plasma protein) + 31 (tissue pressure) = 49 mm. Hg
Force pulling water into tissues:
12 (4% edema fluid protein) + 40 (capillary pressure) = 52 mm. Hg

In this animal, there is a definite preponderance of forces tending to put fluid into the tissues, as one might expect during edema formation.

At the beginning of this century, medical men generally looked hopefully forward to an immunologic specific for every bacterial disease. Unfortunately, however, such specifics are still too few. A surgeon still has no reliable immunologic agents upon which he may depend in the treatment of suppurations. The patient must still fight out the conflict with bacteria with little specific help from chemical irrigating

solutions, and the surgeon must content himself with supporting the natural local and general resistance of the patient in his combat with the invading bacteria. Hirschfelder has shown that no antiseptic agent will penetrate tissue effectively and preserve its antiseptic properties for more than a millimeter.

The relief of pain which attends elevation and rigid immobilization is usually striking. In the last few years, therefore, immobilization and elevation of the infected extremity in plaster have been employed as the primary treatment in a number of acute infections, among which have been cases of infection of joints, bones, and soft tissue. The remote results in the treatment of osteomyelitis, of course, cannot be definitely assayed. The impression has been gained that this method of treating joint infections, when accompanied by proper incision to afford dependent drainage of abscesses, is far superior to the method of active mobilization. Usually, the results attending its use in infections of the soft tissues are superior to those obtained by other means.

CONCLUSIONS

1. Blood flow in an extremity is definitely influenced by its position. This is shown by the fact that (a) elevation reduces the arterial systolic pressure and skin surface temperatures, and (b) dependency increases the arterial systolic pressure and skin surface temperatures.

2. The edema fluid in inflamed extremities of patients is usually under a tension higher than the venous pressure, and often higher than mid-capillary pressure. This entails an elevation of ten to twenty times the normal tissue tension and tends to effect further formation of edema fluid.

3. Immobilization and rest definitely reduce the tissue tension of an inflamed extremity.

4. The elevated skin surface temperatures of inflamed extremities is a criterion of the greater blood flow.

5. In normal young men, gravity may increase the leg volume 2 to 7 per cent during the day. In inflammations of an extremity, the volume may increase as much as 50 per cent.

6. The increased volume of an inflamed extremity can be markedly reduced by elevation.

7. The protein level of edema fluid from inflamed extremities in patients is usually just below that of the plasma and may be as high.

8. Inflammation of an extremity in the rabbit rapidly stimulates the production of edema fluid, frequently approximating in quantity the normal blood volume.

9. The edema fluid protein levels in inflamed extremities in animals approach the blood plasma levels.

10. Heat inflammation in the rabbit effects a rapid drop in the plasma proteins.

11. The edema fluid pressure in experimental inflammation rises rapidly to capillary pressure levels.

12. Capillary blood pressure is increased in the inflammatory site so that there tends to be an equilibrium between:

$$\text{tissue oncotic pressure} + \text{capillary pressure} = \text{plasma oncotic pressure} + \text{tissue pressure}$$

However, the factors on the left of the equation are relatively weighted so that there is a continuous tendency for edema formation.

13. Treatment of infections of the extremities in the University of Minnesota Hospitals over the six-year period, 1934-1939, by immobilization in casts, usually with elevation, gave good results in 72.2 per cent, fair results in 21.6 per cent, and poor results in 6.0 per cent of the cases. Chronic osteomyelitis constituted 48.3 per cent of the cases.

14. Clinical trial suggests that immobilization and elevation are adjunct measures of distinct value in supporting the natural defense mechanisms of the body in inflammations of the extremities. Their use appears to rest on a rational physiologic basis.

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RESUSCITATION IN ADVANCED ASPHYXIA

Role of Positive and Negative Pressure

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INTRODUCTION

ACUTE asphyxia is generally considered to progress in four, more or less, definite phases[3]:

1. *The period of primary apnea,* in which the breath is held, the glottis may or may not be closed in spasm, and a period of shallow breathing may ensue.

2. *The period of dyspnea,* in which the respiratory movements are greatly increased, the accessory muscles of respiration come into play, tonic and clonic convulsions may appear, and the blood pressure rises.

3. *The period of terminal apnea,* in which the respiration has ceased; in exceptional cases, some asphyxial or agonal gasps may be taken. The limbs become limp, the blood pressure falls, but the heartbeat is still definite and regular. For the first part of this period, the heart rate may increase and the pulse pressure decrease. Toward the end of the period, the heart generally becomes slower and irregular, although the pulse may increase. The pupils are dilated and their reflexes gone; the corneas are glassy. Defecation and micturition may occur. At the end of this period the heart rate may again increase, its output diminish, and it is difficult to tell whether the heartbeats are expulsive.

4. *The period of failure of the heart,* in which the heart may fail either in standstill or in ventricular fibrillation (Fig. 1), and death occurs.

In general, each period lasts about a minute. Considerable variation, however, may occur in the time periods and in the characteristics of each phase of asphyxia, especially when an anesthetic has been administered before the start of the experiment.

MODES OF PRODUCTION OF ASPHYXIA

In these experiments, asphyxia was produced either by (1) mechanical obstruction of a face mask or obstruction of an intratracheal tube, or (2) inhalation of inert gases (nitrogen, helium, or nitrous oxide) at the mask or by way of the intratracheal tube, with an inflatable rubber cuff to avoid leakage.

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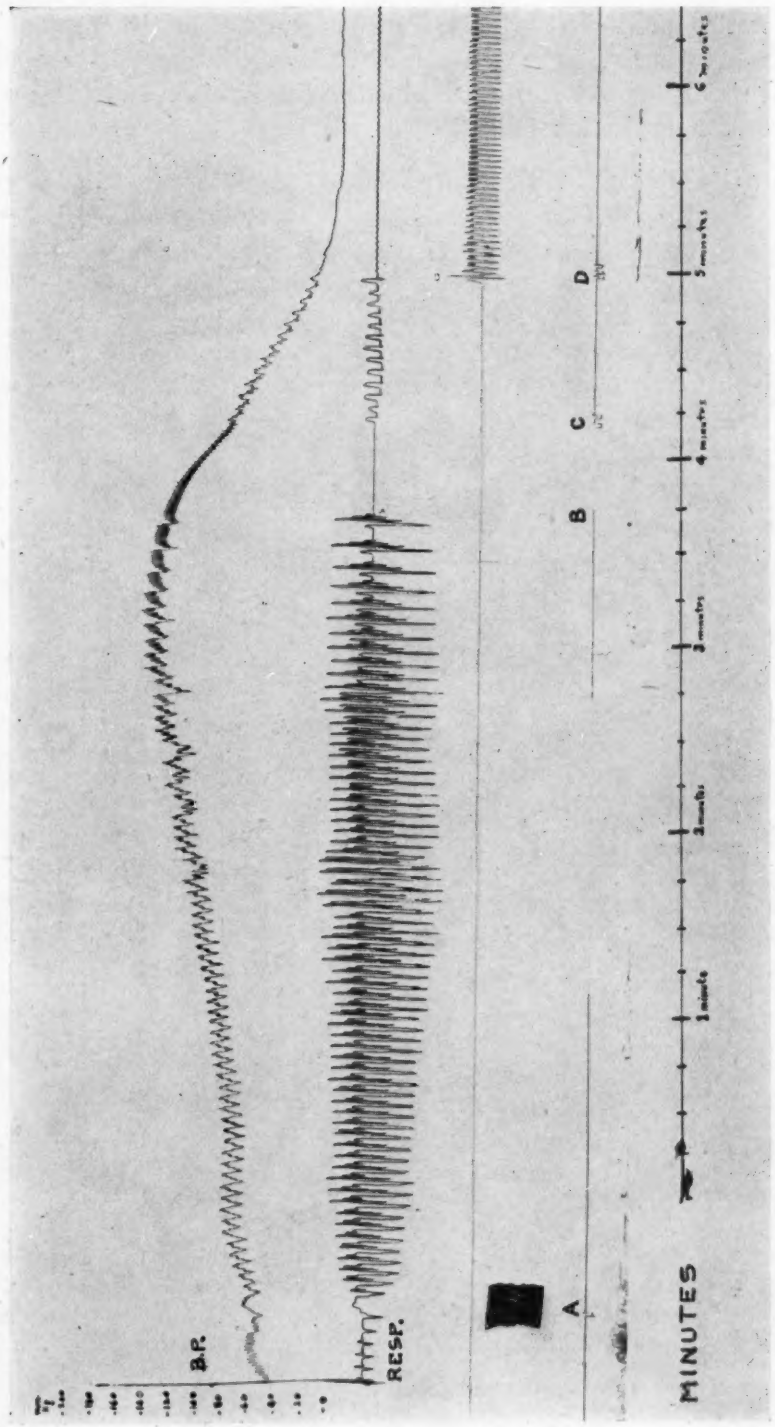

Fig. 1 (Dog 11).—Mechanical obstruction asphyxia at the mask. *A*, Obstruction at mask begun; *B*, respiration ceases; *C*, manual artificial respiration with O_2 started, but was ineffectual; *D*, resuscitator with oxygen started but this, too, was ineffectual at this point.

EVIDENCE OF RESUSCITATION

Resuscitation procedures were carried out by way of the face mask or intratracheal tube. The criteria of successful resuscitation were (1) rapid rise of the blood pressure which was maintained and (2) a return of regular respiration (Fig. 2).

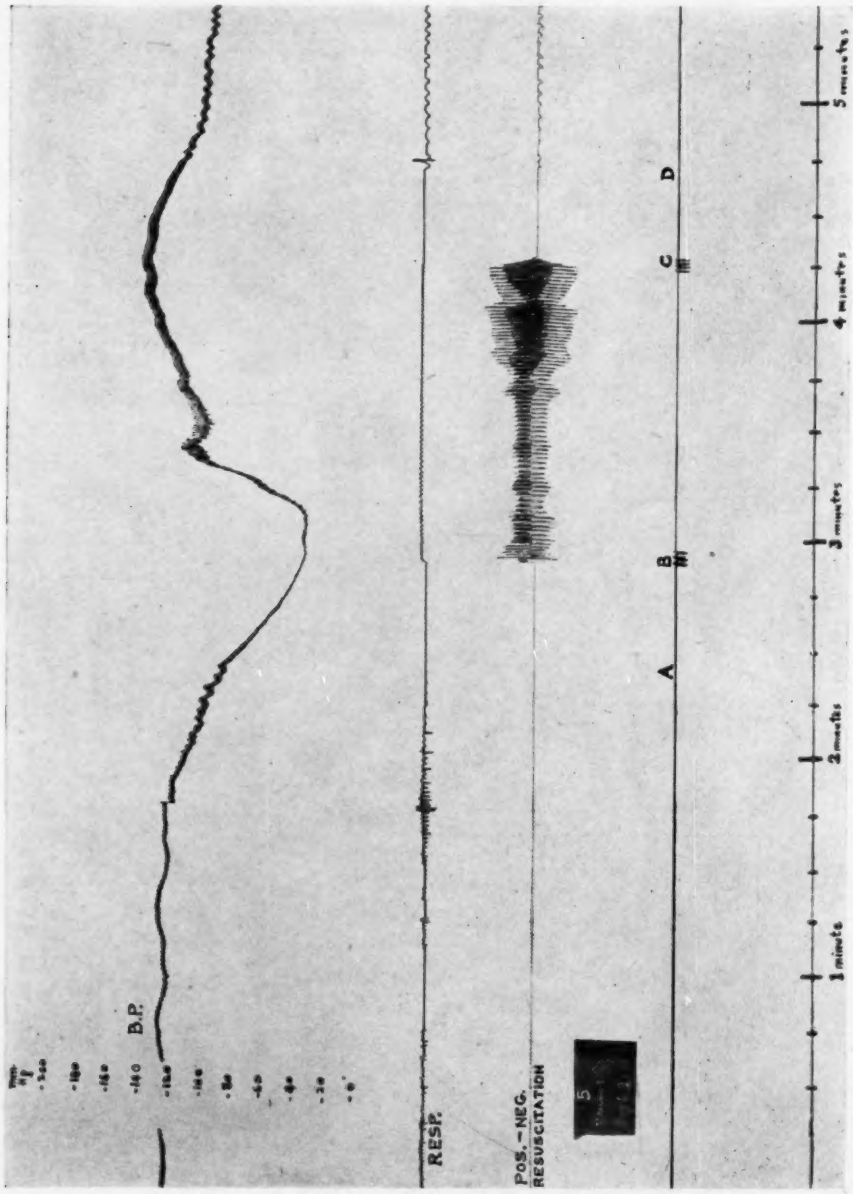

FIG. 2 (Dog 5).—Nitrogen inhalation asphyxia at the mask. *A*, Respiration ceases; *B*, resuscitator with oxygen started; *C*, resuscitator discontinued, mask opened to atmosphere; *D*, spontaneous respiration ensues.

DISCUSSION

In our experiments on animals (dogs), four methods of resuscitation were used:

1. Manual artificial respiration with inhalation of oxygen was carried out by moderately vigorous, side-to-side compression of the lower thorax

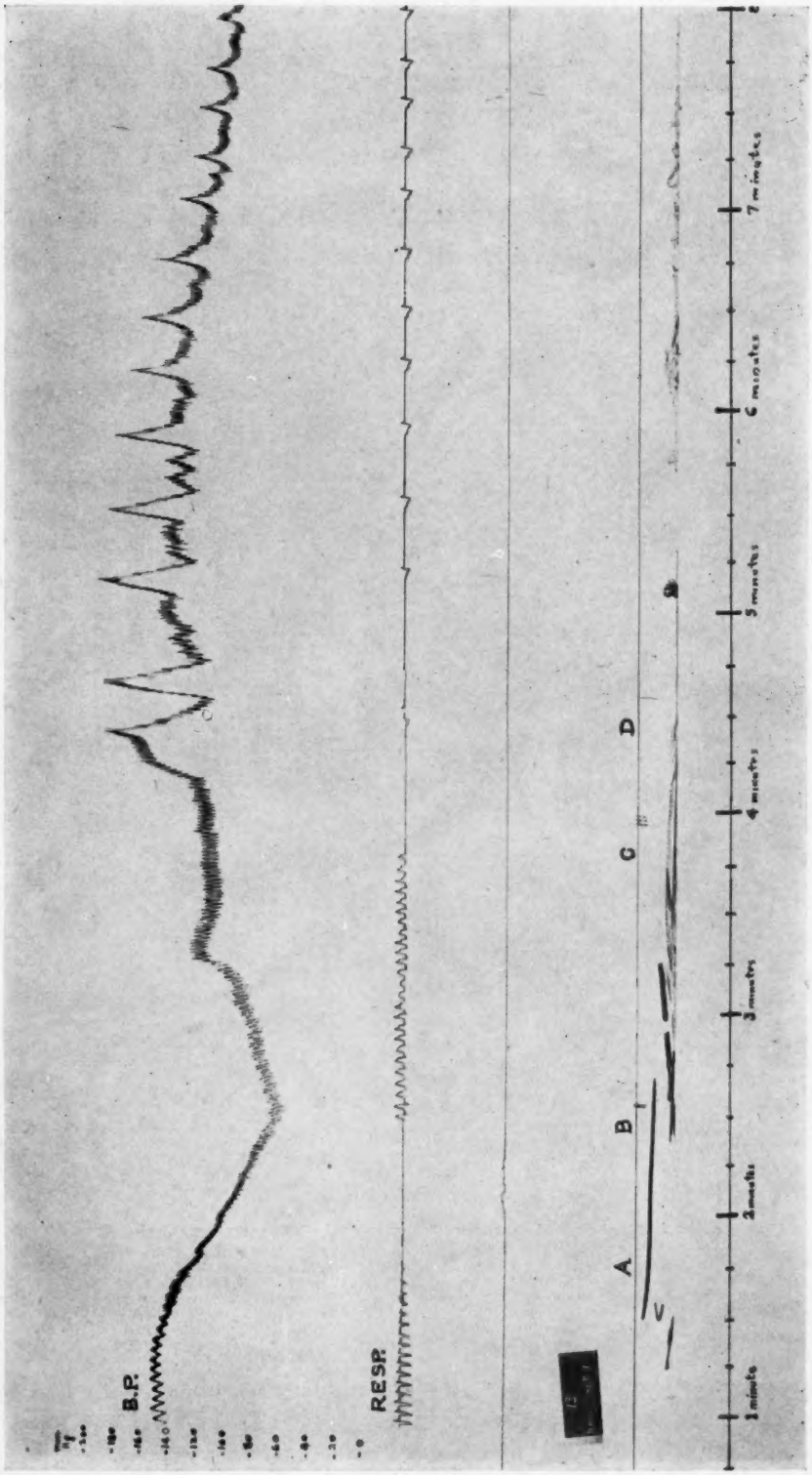

Fig. 3 (Dog 13).—Nitrous oxide asphyxia at the mask. *A*, Respiration ceases; *B* and *C*, manual artificial respiration with oxygen, showing slow recovery of blood pressure; *D*, spontaneous respiration.

by the extended fingers of both hands at the same time the thumbs and thenar eminences of the hands compressed the upper abdomen.

2. The rhythmic inflation of oxygen was carried out at 12 to 15 mm. Hg pressure.

3. Rhythmic suction with oxygen was carried out at 8 to 12 mm. Hg pressure.

4. Mechanical resuscitation* was carried out with rhythmic alternating pressure and suction of +14 mm. Hg and –9 mm. Hg, with oxygen.

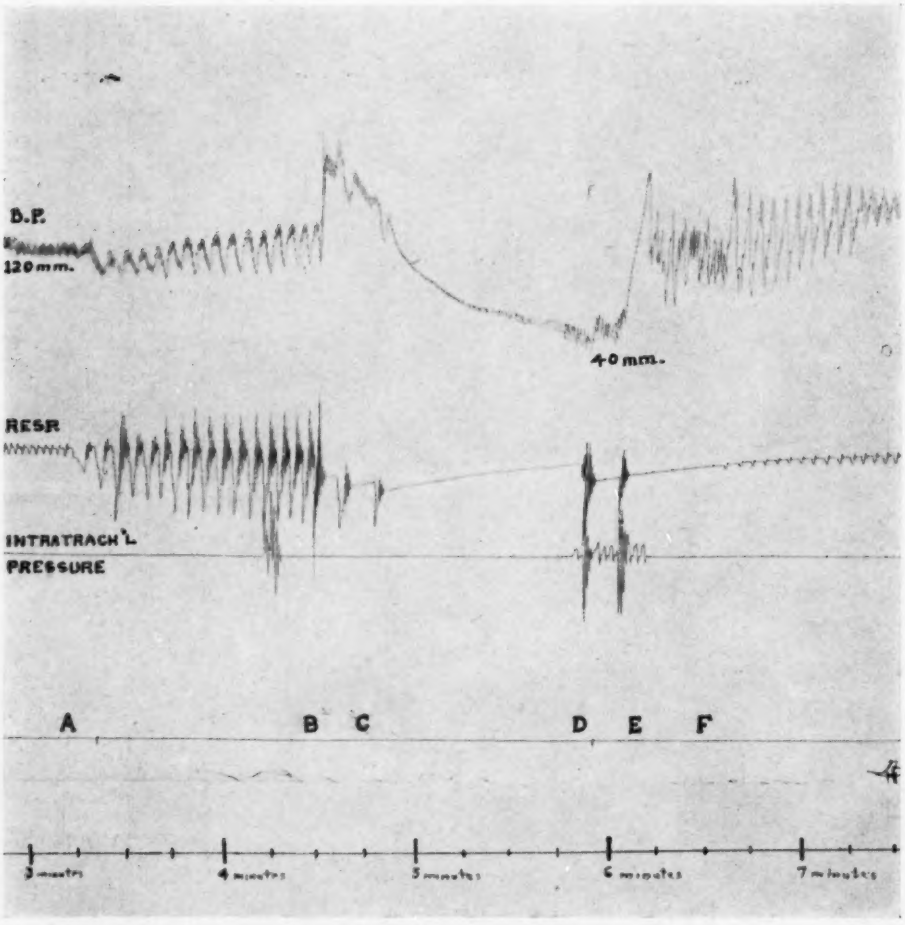

Fig. 4 (Dog 46).—Mechanical obstruction asphyxia at intratracheal tube. *A*, Obstruction of tracheal tube; *B*, drum stopped to conserve space; *C*, respiration ceases; *D* and *E*, rhythmic inflation of oxygen (14 mm. Hg to 0 mm. Hg), notice the immediate stimulation of the respiratory mechanism as evidenced by the greatly increased height of the intratracheal pressure curve; *F*, spontaneous respiration begins.

Table I (left half, oxygen) shows the degree of success obtained by the various methods. It is seen that manual artificial respiration with oxygen inhalation was successful in 55 per cent of the experiments. Rhythmic inflation with oxygen was successful in 78 per cent, rhythmic

*Emerson resuscitator.

TABLE I

SUMMARY OF 106 EXPERIMENTS WITH DIFFERENT RESUSCITATIVE PROCEDURES

	OXYGEN			NITROGEN		
	SUCCESS	FAILURE	PER-CENTAGE SUCCESS	SUCCESS	FAILURE	PER-CENTAGE SUCCESS
Manual artificial respiration	6	5	55	1	6	15
Rhythmic inflation	7	2	78	2	10	17
Rhythmic suction	4	1	80	1	4	20
Resuscitation (rhythmic inflation and suction)	21	1	95	30	5	85

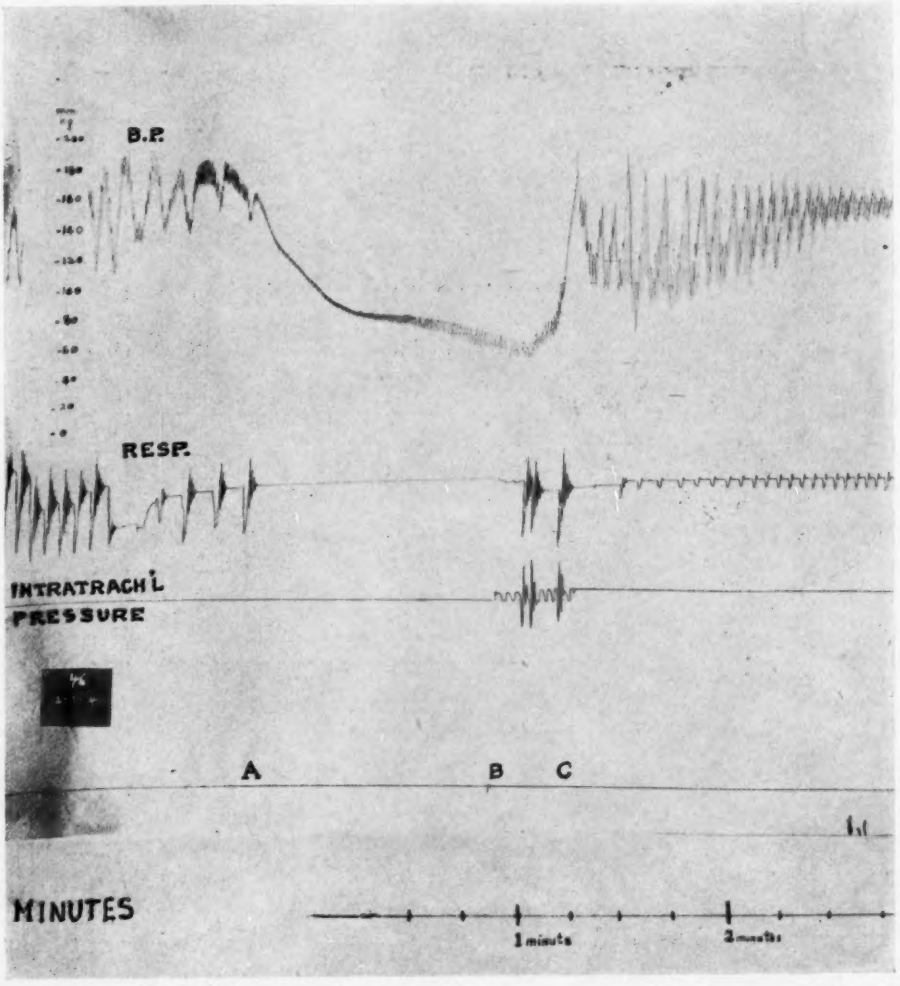

Fig. 5 (Dog 46).—Mechanical obstruction asphyxia at intratracheal tube. *A*, Respiration ceases; *B* and *C*, rhythmic suction with oxygen (−8 mm. Hg to 0 mm. Hg); notice again the sharp rise of the blood pressure, the immediate stimulation of the respiratory mechanism, and the rapidly ensuing spontaneous respiration.

suction with oxygen in 80 per cent, and rhythmic inflation and suction in 95 per cent (Figs. 3, 4, and 5).

Thus, it is evident that either rhythmic inflation alone or rhythmic suction is a valuable resuscitation procedure. The combination of

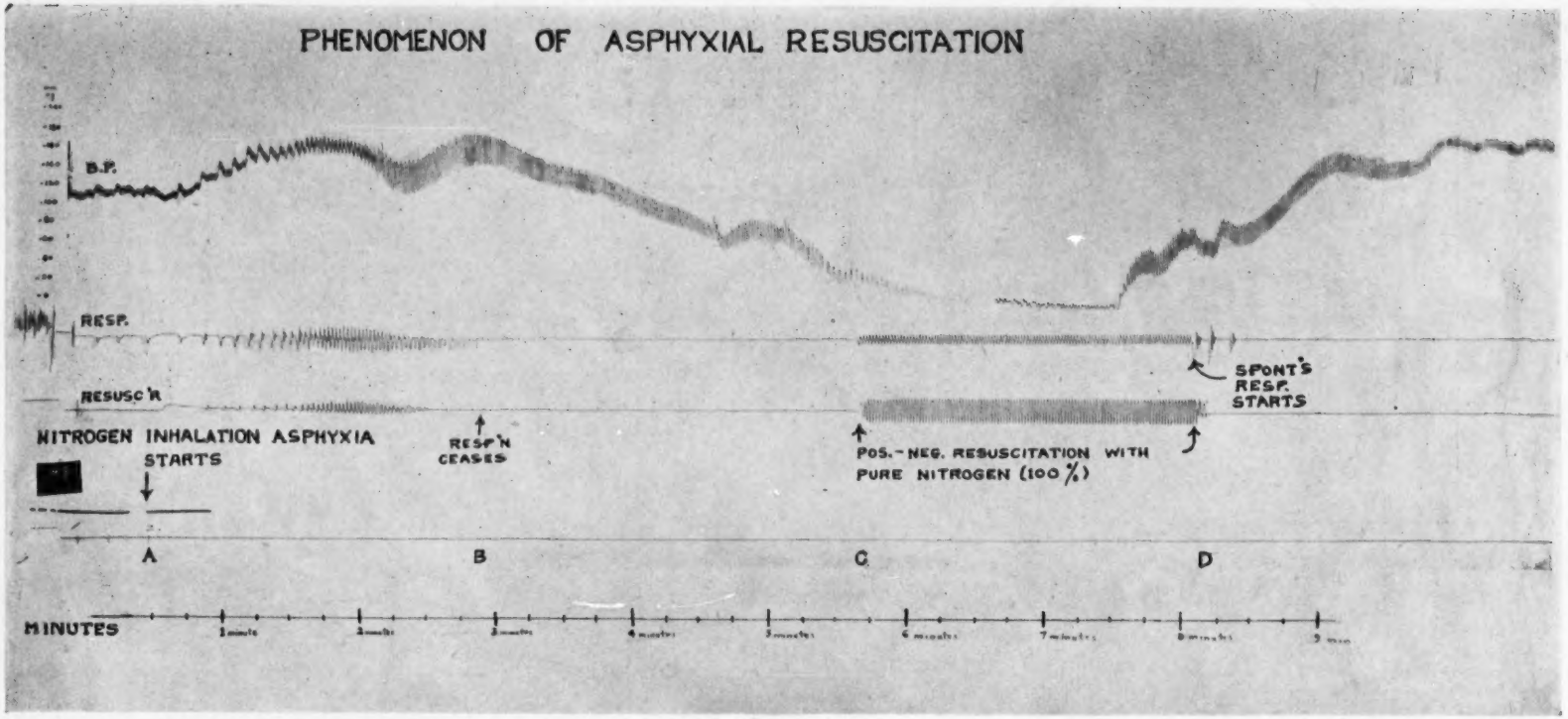

Fig. 6 (Dog 43).—Phenomenon of asphyxia resuscitation. *A*, Nitrogen inhalation asphyxia is started by way of the intratracheal tube; *B*, respiration ceases; *C*, almost 3 minutes after the respiration has ceased, pure nitrogen is administered by the suck-and-blow resuscitator (14 mm. Hg, −9 mm. Hg), and 1¾ minutes later the blood pressure starts to rise; *D*, spontaneous respiration is initiated and the intratrachael tube is opened to the atmosphere.

rhythmic inflation and suction is even more valuable, as can be seen in Table I.

The value of the resuscitation procedure alone without the stimulating effect of oxygen can be demonstrated by attempting to resuscitate with an inert gas instead of oxygen. We have called this resuscitation the Phenomenon of Asphyxial Resuscitation (Fig. 6). It can be produced in a high percentage of instances only with the combination of rhythmic inflation and suction. Using nitrogen, resuscitation can be produced by manual artificial respiration in 15 per cent, by rhythmic inflation in 17 per cent, by rhythmic suction in 20 per cent, and by combined inflation and suction in 85 per cent of the instances where tried. This phenomenon cannot be produced after double vagotomy (Fig. 7).

From the above considerations it becomes clear that in advanced asphyxia with cessation of respiration, the inflation and suction action on the lungs is important in stimulating the respiratory and circulatory mechanisms.

Section of the vagi prevents the occurrence of the phenomenon of asphyxial resuscitation, although resuscitation still may be produced after double vagotomy and asphyxia by using oxygen instead of nitrogen. In the latter instance, resuscitation is accomplished by the factor of oxygen alone, and without the benefit of reflex stimuli.

We wish to emphasize that it is the combination of a reflex from active inflation and a reflex from active deflation which is necessary to produce this phenomenon.

Howell[1] states: "It was found that at each inspiration the galvanometer gave evidence of the passage of afferent nerve impulses, and that when the lungs were forcibly collapsed by active suction a record was obtained which might be accepted as evidence of the discharge of a different set of fibers. More recently a similar result has been obtained by Adrian making use of his special technique. After cutting the vagus high in the neck, he dissected the nerve so as to isolate a small group of fibers having a common origin in the lungs. These fibers were connected with an oscillograph recorder through an amplifier so that a magnified record was obtained of their activity. In this way he was able to show that at each inspiration there is a burst of afferent discharges, the rate increasing as the lungs expand and falling off, perhaps to zero, as they collapse in expiration. This result indicates that there are receptors, stretch receptors, in the lungs which are stimulated mechanically as the lungs expand and in proportion to the degree of expansion, just as the stretch receptors, the spindles, in a muscle are stimulated by stretching it. The histologic character and location of these sense endings in the lungs are still to be determined. It is believed that the afferent impulses thus aroused act to inhibit the inspiratory discharge from the respiratory center and shorten the inspiratory movement. The result is to quicken the respiratory rate, since the center recharges

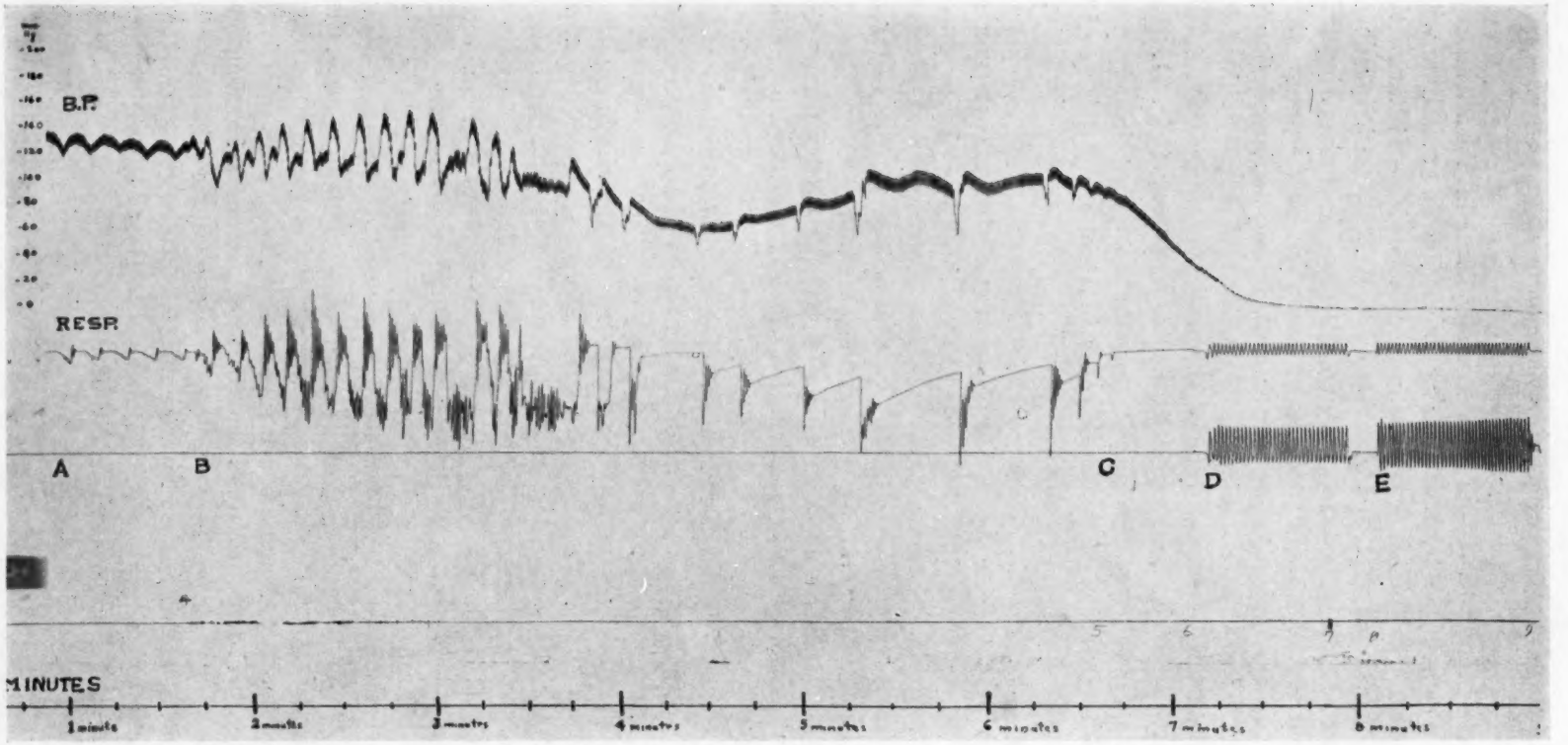

Fig. 7 (Dog 38).—Failure of phenomenon of asphyxial resuscitation after double vagotomy. *A*, Record taken after both vagi were cut in the mid-neck below the level of the carotid sinus; *B*, the intratracheal tube is clamped; *C*, respiration ceases and the blood pressure starts to fall precipitously, which is quite characteristic; *D* and *E*, attempts at suck-and-blow resuscitation with nitrogen fail.

more promptly. The mechanism acts automatically to keep the respirations more rapid and more shallow than would otherwise be the case. It was found also by this method that a sudden suction applied to the lungs set up a burst of afferent discharges, but that this was not the case with the normal passive collapse of the lungs.''

Henderson and Turner[2] do not see the necessity of the suction phase of resuscitation when, for example, asphyxia occurs during an operation on a patient, with the chest open, since the lung is already collapsed. However, we want to point out that there is the *contralateral* lung which is *not* collapsed, and it is principally upon this lung that the benefit of reflex resuscitation depends. This benefit becomes even more important when the chest is opened and one lung is already collapsed. In addition, the suction phase of suck-and-blow resuscitation maintains a more regular pulmonary ventilation, even in the collapsed lung.

CONCLUSIONS

1. Rhythmic inflation and rhythmic deflation (suction) of the lungs each have a very definite and valuable place in resuscitation in advanced asphyxia.

2. The combination of rhythmic inflation and deflation of the lungs with oxygen or carbogen, using safe pressures, is superior to manual artificial respiration, rhythmic inflation alone, or rhythmic suction alone.

The authors are indebted to Dr. Otis M. Cope, Professor of Physiology, and his staff, for their kind cooperation.

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ITALIAN METHOD OF PLASTIC REPAIR OF DENUDED AREAS FOLLOWED BY MERMAID CAST IMMOBILIZATION

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PATIENTS suffering from tender, healed scars of the legs or from denuded areas and ulcers of the legs of recent or remote origin comprise a considerable proportion of those odd refractory cases that, after being passed on from clinic to clinic, at long last reach the orthopedic department. Having experienced too many failures with various methods of conservative treatment, including the usual methods of skin grafting to the lower leg, a method of treatment was sought which would prove more acceptable and more efficient and would assure more successful end results.

The Italian method of skin grafting seemed to be physiologically sound and altogether the most acceptable of the various skin grafting methods. It was first described in 1442 by Brancha of Cateno, Italy, and later by Gasparri Togliacozzi, who popularized the method by publishing a book on pedicle skin grafting in 1597. This voluminous masterpiece contains many beautiful illustrations.

Grafts of various types applied to the tibial surfaces of the leg are only moderately successful and frequently fail. Failure is caused by (1) lack of sufficient bed of subcutaneous tissue; (2) local inanition of the part; (3) inflammatory conditions under which the thin or small grafts cannot survive; (4) mild local infections which destroy the delicate grafts; (5) circulatory causes, such as endarteritis obliterans, localized edema from obstruction to venous return, and capillary deficiency in surrounding scar tissue; and (6) chronic conditions in deeper tissues, such as mildly inflammatory osteomyelitis or osteitis, which constantly present obstacles to the healing of the delicate new grafts.

The advantages of the Italian method of skin grafting are (1) adequacy of size and supply, (2) assurance of viability of the graft through its broad pedicle, (3) easy adaptability to almost any location of the leg or foot, (4) sufficiency of subcutaneous tissue, (5) simplicity of procedure, (6) easy position of patient during the process, and (7) a protecting pad can be placed over bony areas. On the other hand, the disadvantages that may be given are (1) necessity of immobilization for three or four weeks, (2) two operations are necessary, (3) local mild infection with mildly offensive odor may occur, and (4) the difficulty of holding the limbs together at proper approximation for the required time.

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In the past, assiduous attention on the part of the surgeon and all assistants was imperative to maintain proper approximation of the parts without unduly stretching the pedicle of the graft from its donor site or of the sutures at the recipient site. This extreme and tedious cooperation was a sine qua non that spelled success or failure, and to obviate this difficulty a simple form of immobilization and approximation is proposed, namely the mermaid plaster cast.

Method of Procedure.—Two days before operation the defect is inspected and approximated to a healthy area on the opposite calf, usually by crossing the legs. The donor area and pedicle are outlined with dye or silver nitrate stick. The legs are now separated without changing the comfortable angles at which the ankles and knees have been held. After applying requisite stockinet and padding, a plaster cast is applied from the upper thigh to the toes, meanwhile maintaining the original degree of angulation at the knee and ankle. A cast is likewise applied to the opposite leg. A large window is now cut out over the defect and a similar large opening made over the donor site. Through these windows the areas can be adequately prepared.

Operation.—A pedicle flap on the donor leg is incised as previously planned, with a broad base and with ample subcutaneous tissue. By crossing the casted extremities, the donor and defect sites can be approximated and their relative position maintained with ease. The pedicle is sutured in position along the distal and lateral edges, preferably with waxed silk interrupted sutures. By gentle manipulation of the casts the pedicle can be moved so as to be held sufficiently relaxed or taut as necessary. The wounds are dressed with a generous supply of vaseline gauze. If pressure is required on the pedicle in its new bed, a moistened sea sponge can be applied over the vaseline gauze (Fig. 1).

In this easy position, without danger of injury to the graft, the limbs can now be connected with a few rolls of plaster which, when set, will absolutely hold them immobile for the required time, usually from eighteen to twenty-one days. The patient is comfortable and can be turned on his side or face (Fig. 2).

Treatment of the Pedicle Graft.—At its new site, after severance and separation at the base, the properly planned pedicle will amply cover the defect. Trimming of the base and edges may be necessary so that proper application of skin edges may be secured. The edges of the three sides formerly sutured have formed a firm union in their new position. The base is now sutured in position with one or two small drains inserted. The subsequent treatment demands meticulous care because this flap is a delicate new-born, is mildly edematous, and requires constant gentle pressure which is just sufficient to prevent swelling but does not produce anemia. Mild external radiant heat is applied from a covered overhanging lamp.

Treatment of the Donor Site After the Second Stage of Operation.—Due to elastic contracture of the surrounding skin, the donor site defect may be considerably larger than the area first outlined (Fig. 3). Nevertheless, the base is of muscle and fascia with abundant blood supply. It is covered with pinch grafts from the thigh or adjacent calf. All of these usually survive and complete epithelialization of the intervening spaces occurs in less than two weeks' time (Fig. 4).

After the pedicle has been cut, the casts are removed and left off.

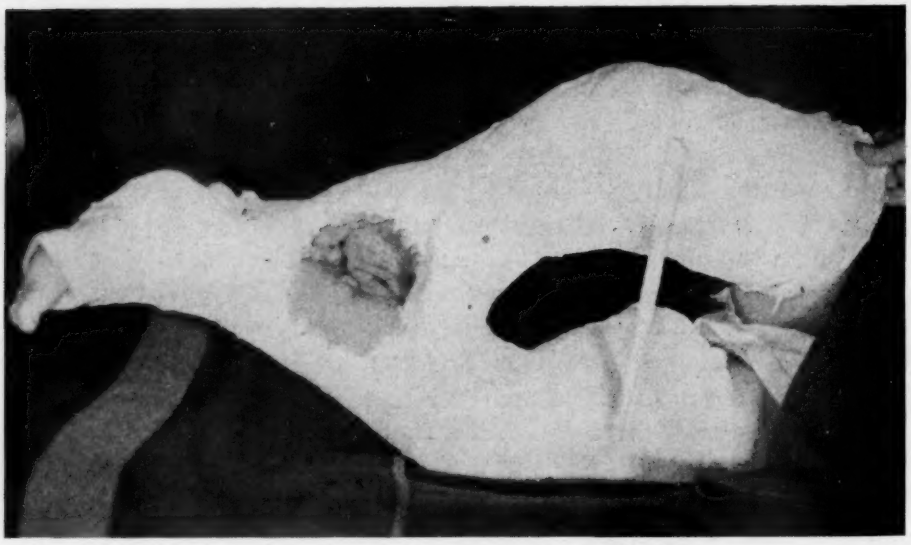

Fig. 1.—Pedicle graft in position before separation.

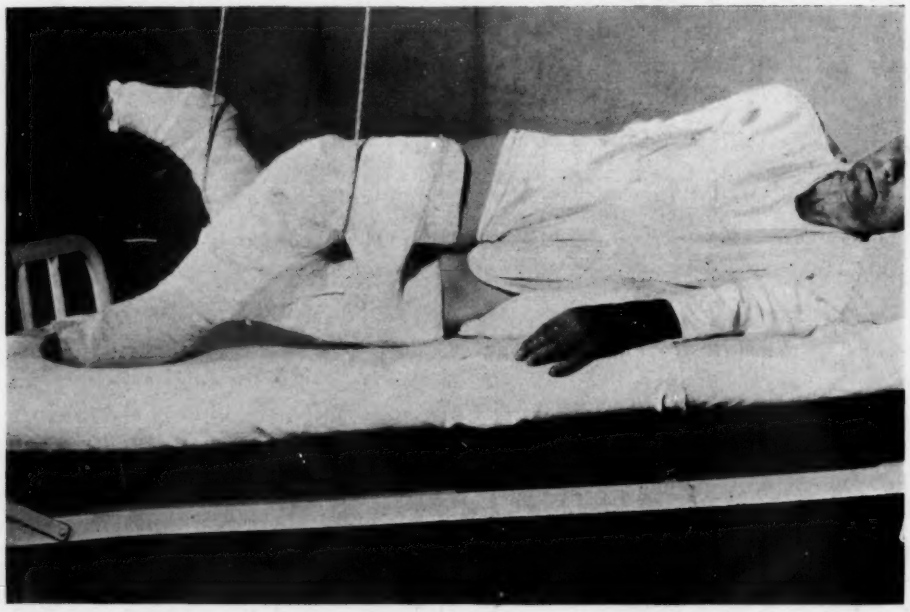

Fig. 2.—Showing position of patient in bed after the first operation. Note the angulation of the legs.

COMMENTS

In the application of any pedicle graft certain general broad rules must be followed, but deviation from strict adherence to a rule may be necessary occasionally. To maintain nutrition of the flap from the beginning, the subcutaneous connective tissue, including the superficial fascia, must be included because, as Kirschner states, the arteries supplying the skin run in this connective tissue. Regarding nutrition of the flap, it makes little difference whether a flap be pedunculated distally

Fig. 3.—Donor site on right leg.

or proximally, but it is pedunculated proximally whenever possible. It is more important for incision lines to follow tension lines than lines of lymphatic or vascular supply. Those lines on the posterior surface of the leg run in an obliquely longitudinal direction from above and outward to below and inward. Adherence to this principle is not so essential if the flap is a broad one, but if it is a long narrow one in which the skin edges can be undermined and drawn together at the second

stage, adherence to this principle is advisable. If tension lines are followed, little evidence of scar contracture results.

The area to be incised must first be carefully and deliberately planned, always remembering that shrinkage of the pedicle takes place between the initial operation and the second stage and during the healing process in its new bed. This is more pronounced in the young. The use of a dye or silver nitrate stick to outline the proposed incision obviates haphazard guesswork at the time of operation. Excessive torsion and undue stretching of the flap should be avoided so that

Fig. 4.—Photograph showing scars from pinch grafts used to fill in donor site.

exchange of tissue fluids may be facilitated. The base of the pedicle should be broader than the outline of the flap itself so as to assure continued viability of the graft.

Preparation of the Bed.—Since there is a wide variance in the type of case suitable for pedicle skin grafting, no absolute procedure can be dogmatically laid down, but the following measures are strongly advised.

Denuded ulcers should be treated conservatively until there is a minimum of infection present and until the base is covered with healthy granulations.

Ulcers exposing the bone of the tibia should be treated conservatively until the bone is covered with healthy granulations.

In *scar formation over large areas of the tibia* the thin, delicate, superficial epithelial covering should be excised first so that defect edges extend to healthy surrounding tissues.

In *scars from recurrent osteomyelitis* the underlying condition as well as the underlying unhealthy bone should be treated first. The administration of sulfonamides has met with spectacularly successful results by Hoyt of Akron and their use is indicated.

Indolent ulcers with malignant tendency should be rather widely excised before grafting.

Defects of areas following compound fractures from a strictly orthopedic standpoint comprise a considerable proportion of the cases which are suitable for the proposed procedure. The recent fracture should be treated until osseous repair has been established. The nonunion may necessitate a skin graft procedure before a bone graft operation can be attempted with reasonable assurance of success.

CASE REPORTS

CASE 1.—A. M., an 18-year-old girl, was admitted to the Cook County Hospital, April 1, 1937, because of an ulceration over the internal side of the right ankle measuring 3 by 2 inches, and swelling, redness, and stiffness of the lower leg and ankle. The diagnosis was chronic ulceration of the leg due to an old healed osteomyelitis, and extensive scar formation.

Casts were applied and fenestrated as has already been described. Then the ulceration was completely excised through the surrounding scar tissue. The base of the ulcer was greatly curetted. A pedicle flap pedunculated proximally was incised on the calf area of the left leg. This extended through the skin and superficial fascia down to the deep fascia. It was lifted, the legs were crossed, and the graft approximated to the defect on the right leg. The distal and lateral edges of the graft were sutured into the corresponding edges of the defect with interrupted waxed silk sutures. A vaseline gauze dressing was applied and some soft sponges packed in to give moderate pressure. By manipulation of the casted extremities, the pedicle could be loosened the desired amount. There was no tension and circulation seemed to be adequate in the graft. In this easy position, with a few rolls of plaster of Paris, the casted extremities were immobilized.

The second stage operation was performed, April 24. At this time the base of the pedicle was severed, the legs were separated, and the casts removed. The proximal edge of the skin graft was trimmed, fitted neatly into the proximal edge of the defect, and sutured with black silk. It was found that the three edges had grown in their new position and that a portion of the base had become adherent. Pinch grafts were applied to the donor area on the calf. Vaseline gauze dressings were applied to the pedicle graft with moderate pressure, the leg elevated, and mild heat applied.

Dressings were inspected one week later and on May 8, when the dressings were changed, the graft was noted to be a 100 per cent "take." The patient was allowed up one week after this; there was slight discharge from one sinus

under the graft, which subsequently closed. Since that time it has remained healed; the ulcer is covered and there is ample pad over this portion of the tibia.

CASE 2.—W. G., male, aged 19 years, was admitted to the Cook County Hospital, March 17, 1937, because of an ulceration over the middle third of the left tibia on the anterior surface, and extensive scar formation and tenderness over the middle two-thirds of the same leg. Operation was performed and mermaid casts applied as has been described. The postoperative course was uneventful and the patient tolerated the casts without any complaint.

CASE 3.—S. S., a colored man, aged 26 years, entered the Cook County Hospital, May 15, 1937. He had a flexion contracture of the wrist due to scar formation from an old forearm wound. Since this scar involved the skin and deeper tissue, it was thought that anything less than resection of the whole scar would not result in release of the contracture, therefore, resection of the scar with subsequent pedicle graft was advised. The day before operation the forearm was placed in a plaster of Paris cast and a large window cut over the proposed site of operation. Through the window, operation was performed, taking a pedicle from the abdomen. Position was maintained by extending a cast from the forearm around the body.

The postoperative caurse was uneventful. No inspection was made because the arm and body were encased in a cast. The second operation was performed fifteen days after the first, and the second postoperative course was uneventful. The flap took very well. Under physiotherapy the movement in the patient's fingers returned to 75 per cent. When the graft healed there was still some contracture of the fingers with the hand and wrist held at 180 degrees. A series of plaster casts was applied to the forearm and fingers, gradually stretching them to full extension by the end of two months (Fig. 5).

CASE 4.—F. D., a 58-year-old man, was admitted to the Cook County Hospital, April 19, 1938, because of an ulceration on the lower portion of the internal surface of the left foot. The examining room diagnosis was a squamous cell carcinoma at the base of the left toe. Casting and operation were performed, then a Thiersch split skin graft was applied to the area denuded by the pedicle. Vaseline gauze dressings were applied to both areas with moderate pressure of fluffed sponges over the pedicle graft. Both were immobilized in this position with a few rolls of plaster of Paris and held in position until set. The second stage operation was performed under general anesthesia. The pedicle skin graft flap from the right leg onto the medial side of the left leg was severed at the base of the flap; it was entirely viable and there were no areas of sloughing.

The patient was discharged on June 16. He returned to the clinic first at weekly intervals, later every two weeks. There was no recurrence of the ulceration and the deep tissues were healthy. Six months postoperatively there was little or no swelling and the part had assumed almost a normal appearance. The pathologic report was a squamous cell carcinoma ulceration. The condition of both the donor and defect sites was very satisfactory eighteen months after operation.

CASE 5.—E. H., a man aged 47 years, was admitted to the Cook County Hospital, June 28, 1938, with a chronic ulceration over the upper third of the left tibia on the anterior surface. He had a compound fracture of the left tibia in 1929, with infection of the bone and subsequent osteomyelitis. Six months later the bone was scraped. The donor site on the right leg was quite accessible and was covered with a Thiersch graft from the thigh area. The graft took and ultimately the entire area filled in from the edges.

CASE 6.—R. P., a white boy, aged 9 years, was admitted to the South Shore Hospital, July 9, 1938, following an injury. He had a traumatic defect on the lower right leg measuring 4 by 2 inches. Operation was performed and pedicle skin grafts were applied through windowed casts.

Eighteen days after the initial operation the second one was done. Split thickness Thiersch grafts from the left thigh were applied to the defect in the calf and vaseline gauze dressings applied.

The postoperative course was uneventful; all the graft lived but it shrunk somewhat from the proximal suture line inserted at the second operation.

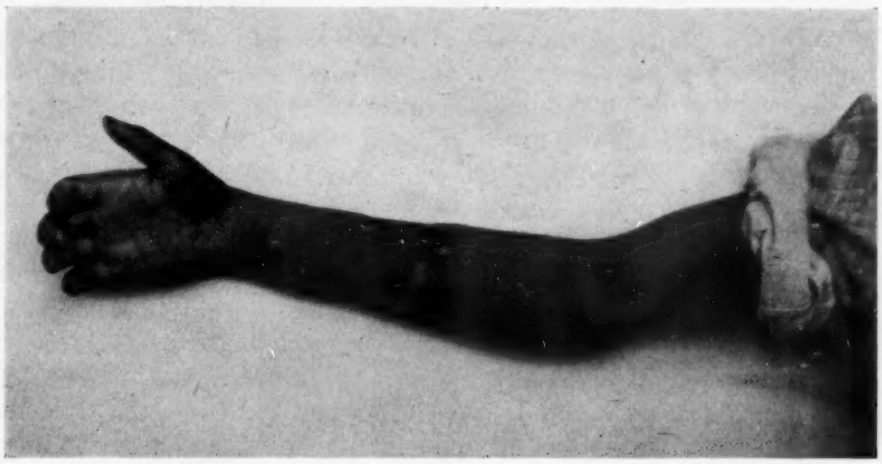

Fig. 5.—Final result; note the extension present in arm and fingers.

CASE 7.—W. G., male, aged 21 years, was admitted to the Cook County Hospital, Feb. 21, 1939, with a case of osteomyelitis for which many operations had been done. Two years previously he had had a skin graft with a mermaid cast, with excellent results. At this time he had another area of ulceration due to breaking down of the old scar at a new position. The patient was prepared and operated upon according to the technique already described. The postoperative course was uneventful; the patient tolerated the immobilization without complaint. The second operation was also performed without difficulty and the patient was discharged from the hospital April 12, 1939, with an excellent result. He was seen again in December, 1939, and the graft was found completely healed.

CONCLUSIONS

1. Denuded areas on the legs and feet present a definite problem in orthopedic clinics.

2. The Italian method of skin grafting has been found to be a relatively safe and successful procedure for their care.

3. Mermaid cast immobilization facilitates the operative procedure and the postoperative care.

4. Seven cases are presented in six patients and results illustrated by photographs.

THE EFFECT OF LOW BLOOD PRESSURE UPON CAPILLARY PERMEABILITY AND INFLAMMATION IN THE SKIN OF RABBITS*

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ONE of us (R. H. R.) has been interested in the factors that influence capillary permeability and inflammation in the skin of the rabbit. The mechanism by which increases in capillary permeability may occur has been discussed frequently.[1-3] The localization and the concentration of certain colloidal dyes following intravenous injection has been used to demonstrate changes in capillary permeability. An increase in capillary permeability occurs when the dye localizes and concentrates more quickly in one area of skin than it does in another in the same animal.

Trypan blue injected intravenously localizes and concentrates in areas of inflammation produced by xylol in the rabbit.[4] The time required for the localization of the dye and the quantity of dye that localizes and concentrates in an area of inflammation is influenced by the interval between the application of the irritant and the injection of the dye. The greatest quantity of dye localizes and concentrates in the area where xylol is applied the shortest time before the dye is given. There is a progressive diminution in the quantity of dye that concentrates in xylol-treated areas when the interval between the application of xylol and the injection of the dye is progressively increased. When xylol is applied three hours or longer before the dye is injected, essentially the same amount of dye localizes in the xylol-treated areas as in the untreated skin.[4]

Macroscopic and microscopic observations are made in the studies on inflammation and the presence or absence of leucocytes about the irritants is considered significant. The relationship of capillary permeability, as defined above, to the presence of polymorphonuclear leucocytes in areas of inflammation has been discussed.[3]

Capillary permeability and inflammation have been studied in narcotized rabbits.[5] Capillary permeability in areas of inflammation is altered in rabbits narcotized with both alcohol and ether as demonstrated by the localization and the concentration of trypan blue. The inflammatory response may be either greatly diminished or only slightly decreased in rabbits narcotized with alcohol and ether, as indicated by the amount of hyperemia, edema, and the number of leucocytes that

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localize in response to both chemical and bacterial irritants. It is interesting to note the similarity of the effect of adrenalin to narcosis on capillary permeability and inflammation in the skin of the rabbit.[7]

Adrenalin when given intradermally and intravenously in large quantities inhibits the development of hyperemia in areas of skin where xylol is applied. Trypan blue when given intravenously, fails to localize and to concentrate in areas of the rabbit's skin where adrenalin is injected intradermally and xylol is applied locally, although the areas become reddish brown in color after twenty to thirty minutes.

Capillary permeability and inflammation have been studied in rabbits with staphylococcal septicemia.[7] It was noted that capillary permeability and inflammation, as observed in the skin, is different in a rabbit with a staphylococcal septicemia from that in a normal rabbit. This variation apparently may be the result of constriction of small cutaneous blood vessels. This reaction in the skin is similar to that which may occur in rabbits anesthetized with either alcohol or ether, or injected with large quantities of adrenalin.

An experimental study of capillary permeability and inflammation in rabbits with lowered blood pressure is considered important in view of the previous experiments and the subsequent observations to be reported on capillary permeability and inflammation in shock.

METHODS AND MATERIALS

In our experiments rabbits are used. The blood pressure is recorded from the carotid artery either by a mercury manometer or on a kymograph. The tissues in the neck are anesthetized with a 1.0 per cent solution of novocain. A 1.0 per cent solution of sodium citrate is used as the anticoagulant in washing the cannula and the tubing. The length of time during which the animals are observed in these experiments varies from an hour to six hours.

The arterial blood pressure is lowered either by removing blood through the cannula or by bleeding directly from the heart. Sometimes multiple small bleedings are made, while in other experiments a single large volume of blood is removed. The quantity of blood to be removed is determined by the level of the blood pressure.

The skin is shaven carefully twenty-four hours or longer before the experiment is begun. Xylol is applied carefully to local areas of skin at varying intervals before 10.0 to 15.0 c.c. of a 0.2 per cent solution of trypan blue is injected intravenously in those experiments where capillary permeability is studied. The time and the amount of dye that localizes in the different areas of skin is recorded.

Macroscopic and microscopic observations are made on the xylol-treated areas of the skin, the areas injected intradermally with a heavy saline suspension of staphylococci, and also with a 2.0 per cent suspension of aleuronate. Sections of the skin are removed at different inter-

vals following the injection of the irritants. They are fixed in a 10 per cent solution of formalin. Paraffin sections are prepared and stained with hematoxylin and eosin.

OBSERVATIONS ON CAPILLARY PERMEABILITY IN THE SKIN OF RABBITS WITH A LOW BLOOD PRESSURE

Seventeen rabbits are used in this experiment. A majority of these are adult rabbits weighing from 1.5 to 3.0 kg. A few young rabbits are used.

It is difficult to standardize the experimental procedure since the degree of the fall in blood pressure varies so widely in the different rabbits. The following protocols are selected to illustrate the changes observed in the localization of trypan blue in adult rabbits:

Rabbit X-1

2:45 P.M. Cannula put into carotid; blood pressure, 144.
2:44 P.M. 40 c.c. of blood removed through cannula; blood pressure, 48.
3:05 P.M. Blood pressure, 128; 10 c.c. blood removed.
3:10 P.M. Xylol applied to the skin in area 1.
3:20 P.M. Xylol applied to the skin in area 2.
3:30 P.M. Xylol applied to the skin in area 3. The skin in area 1 has a reddish brown color.
3:30 P.M. Xylol applied to the skin in area 4; blood pressure, 98.
3:50 P.M. Xylol applied to the skin in area 5.
3:55 P.M. Xylol applied to the skin in area 6.
4:00 P.M. There is no hyperemia in areas 3, 4, 5, and 6. Xylol applied to the skin in area 7; 15 c.c. trypan blue given intravenously.
4:05 P.M. No dye has localized in any of the xylol-treated areas of the skin.
4:20 P.M. Areas 1 and 2 are reddish brown in color and there are small blue spots in the area. Trypan blue is present at the periphery of the xylol-treated skin.
4:25 P.M. A small amount of dye is present in areas 5 and 6.
4:40 P.M. There is a diminution in the intensity of the reddish brown color from area 1 to area 7. There is no dye in area 7.
4:45 P.M. Little spots of dye are present in areas 1, 2, 3, and 6.

In rabbits with normal blood pressure the dye usually appears in the last area of skin treated with xylol within a period of five minutes. In these rabbits with lowered blood pressure, the time required for the dye to localize is much longer and sometimes it fails to localize. The localization of the dye at the periphery instead of within the xylol-treated area has never been observed in the normal rabbit. Blue areas 1 to 2 mm. in diameter, in the xylol-treated areas, have not occurred in the rabbits with normal blood pressure. The dye localizes and concentrates in the skin in a uniform manner in the normal rabbits where xylol is applied.

Frequently there is no hyperemia after the application of xylol to the skin of rabbits with low blood pressure. Hyperemia occurs 15 to 30 seconds following the application of this irritant in normal animals. Edema rapidly follows the hyperemia and both remain for several days.

A reddish brown color similar to that observed in rabbit X-1 has been observed and described in other experiments.[6]

Rabbit X-22

4:20 P.M. Cannula put into carotid; blood pressure, 140.

4:25 P.M. 30 c.c. of blood removed from heart; blood pressure, 50. The skin over the entire body is pale.

4:30 P.M. Xylol applied to the skin in area 1.

4:34 P.M. There is no hyperemia of the skin in area 1.

4:35 P.M. Xylol applied to the skin in area 2.

4:40 P.M. Xylol applied to the skin in area 3.

4:42 P.M. No hyperemia or edema in any of the xylol-treated areas of the skin.

4:45 P.M. Blood pressure, 80.

4:50 P.M. Xylol applied to the skin in area 4; blood pressure, 88.

4:54 P.M. Xylol applied to the skin in area 5.

5:00 P.M. Xylol applied to the skin in area 6; 10 c.c. of trypan blue given intravenously.

5:15 P.M. There is no dye in any of the xylol-treated areas.

The pale appearance of the skin immediately following the withdrawal of blood would suggest constriction of the cutaneous vessels. The absence of the development of hyperemia and edema in the skin of this rabbit and the failure of trypan blue to localize within a period of fifteen minutes is certainly different from the reaction in the normal rabbit.

The following protocol illustrates the variation in the localization of trypan blue in rabbits with a lowered blood pressure as compared with the normal.

Rabbit X-2

3:15 P.M. Blood pressure, 120.

3:35 P.M. 20 c.c. blood removed through the cannula.

3:45 P.M. Blood pressure, 70.

3:50 P.M. Xylol applied to the skin in area 1.

4:00 P.M. Very little hyperemia is present in area 1.

4:15 P.M. Xylol applied to the skin in area 2; blood pressure, 74.

4:22 P.M. No hyperemia is present in area 2.

4:45 P.M. Xylol applied to the skin in area 3. The skin in areas 1 and 2 is a little reddish brown.

5:10 P.M. Xylol applied to the skin in area 4; blood pressure, 56.

5:15 P.M. Xylol applied to the skin in area 5.

5:18 P.M. Xylol applied to the skin in area 6; 10 c.c. of trypan blue given intravenously.

5:20 P.M. Blood pressure, 74.

5:25 P.M. A little dye is present in area 3.

5:27 P.M. A little dye is present in areas 2, 3, and 4.

5:40 P.M. The largest amount of dye is present in area 3. Approximately the same amount of dye is present in areas 2 and 4, less dye in area 5 than in area 4, and less in 6 than in 5. There are approximately a dozen small blue areas 1 to 2 mm. in diameter in area 1.

6:00 P.M. The quantity of dye is gradually increasing in areas 5 and 6. There is about the same amount of dye in areas 4 and 6, only a little in 2 and none in 1 except for the small pinpoint collections. There is no trypan blue in the untreated skin of this rabbit.

All rabbits do not show so great a variation in the time in which trypan blue localizes in the xylol-treated areas as compared with a normal adult animal. The following protocol illustrates the localization of trypan blue in xylol-treated areas of a normal rabbit.

Rabbit 5

1:55 P.M. Xylol applied to the skin in area 1.
2:10 P.M. Xylol applied to the skin in area 2.
2:25 P.M. Xylol applied to the skin in area 3.
2:40 P.M. Xylol applied to the skin in area 4.
2:45 P.M. The xylol-treated areas of skin are hyperemic and edematous.
2:53 P.M. Xylol applied to the skin in area 5.
3:10 P.M. Xylol applied to the skin in area 6; 10 c.c. of trypan blue given intravenously.
3:13 P.M. Dye is present in areas 5 and 6, the greatest amount being in area 6.
3:25 P.M. The greatest amount of dye is present in area 6, with a progressive decrease in the quantity in areas 6 to 1.

MACROSCOPIC AND MICROSCOPIC EVIDENCES OF INFLAMMATION IN RABBITS WITH LOW BLOOD PRESSURE

In the preceding experiments it was shown that the skin of rabbits with low blood pressure may fail to become hyperemic following the application of xylol. Twenty rabbits are used in this experiment to study the inflammatory reaction. The normal arterial pressure is determined in fourteen of the animals before bleeding and at varying intervals thereafter. Six of them are used as controls. All the rabbits are injected intradermally with a suspension of both staphylococci and aleuronat six hours, four hours, and two hours before they are killed. Xylol is also applied to other areas of skin at the same intervals.

There is a wide variation in the arterial pressure in these animals. However, there always appears to be a relationship between the arterial pressure and the macroscopic evidences of inflammation. When the pressure is around 60 mm. Hg there is a definite decrease in the amount of hyperemia and edema and a diminution in the number of leucocytes which localize in the tissue. These changes are nicely illustrated by rabbit 336 in which the decrease in the number of leucocytes is very conspicuous (Fig. 1*A*). The control for this animal shows a diffuse infiltration of the tissue with polymorphonuclears (Fig. 1*B*). Leucocytes may fail to localize about both staphylococci and particles of aleuronat when the blood pressure is lower than 50 mm. Hg. No macroscopic reaction occurs in the skin of rabbit 336 following the injections of the irritants and essentially no polymorphonuclear leucocytes are present in the histologic section.

DISCUSSION

The observations made in this study show that the reactions in the skin are different in a rabbit with low blood pressure from those of a normal rabbit. Xylol may fail to produce any hyperemia in the skin

of rabbits with low blood pressure. Polymorphonuclear leucocytes may also fail to localize in the corium in such animals. Trypan blue injected intravenously may also fail to localize and to concentrate in the xylol-treated area of skin. All of these variations suggest that the small blood vessels constrict in the skin of rabbits following removal of blood and when in this state they fail to react to the local applica-

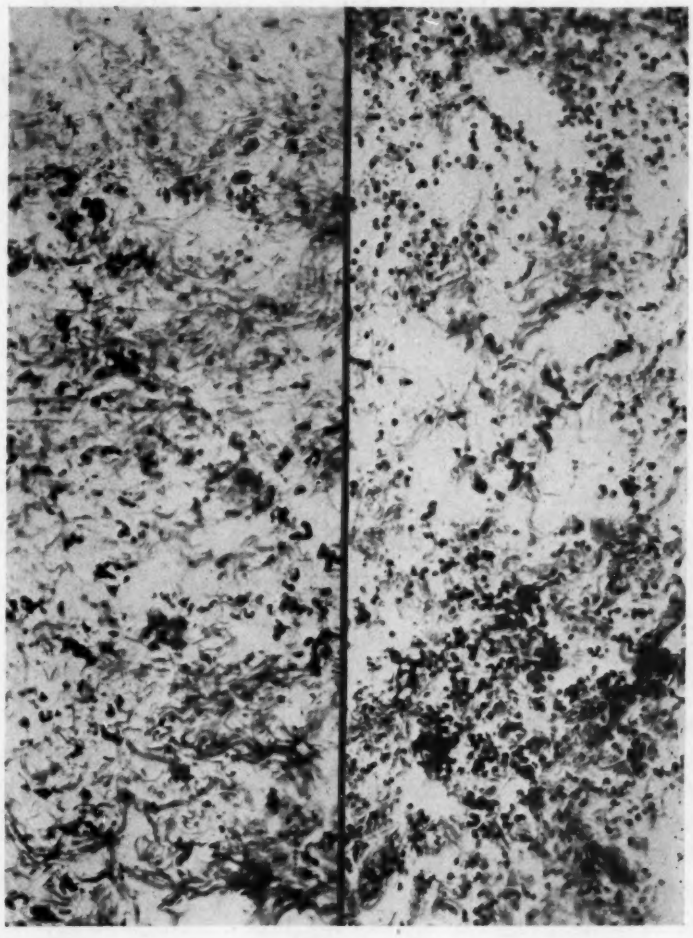

Fig. 1.

A.—Rabbit 336. Cannula put into carotid artery. B.P., 106 mm. Hg; 20 c.c. blood removed through cannula; B.P., 76 mm. Hg; 0.2 c.c. of a saline suspension of staphylococci injected I.D.; B.P. after 6 hours, 14 mm. Hg. Section of skin removed six hours after bacteria injected. Note the absence of leucocytes about the groups of bacteria. The pressure is recorded on a mercury manometer.

B.—Rabbit 337. B.P. not taken; injected the same as rabbit 336. Leucocytes are infiltrating the tissue around the clumps of bacteria.

tion of xylol. Furthermore, since they are constricted, trypan blue and polymorphonuclear leucocytes cannot reach the area of the irritants. It was thought that a vascular constriction of the small vessels in the skin occurred in rabbits given large amounts of adrenalin both intravenously and intradermally. Because of this constriction, hyper-

emia failed to occur and trypan blue did not localize following an intravenous injection.[6]

The variation in the time required for trypan blue to localize and to concentrate in xylol-treated areas of skin in rabbits with low blood pressure as compared with the controls is also interesting. If trypan blue localizes and concentrates in xylol-treated areas of skin as the result of a metabolic change in the cells, then the rate at which this change occurs is influenced by the acute loss of blood.[5] The changes in the epithelial cells in the skin following the application of xylol are much slower in rabbits with low blood pressure. It must be remembered that each of these observations on the localization and concentration of trypan blue in xylol-treated areas of skin is made in the same rabbit.

The observations made in this experiment are more significant when it is recalled that trypan blue localizes and concentrates in one area of the skin and not in another when both are treated exactly alike. This variation results from the difference in the time that the xylol is applied to the areas and the dye is injected intravenously. The quantity of dye in the circulating blood progressively decreases following inoculation. This factor, however, apparently will not explain either the variations in the localizing of the dye in the different xylol-treated areas of skin in a normal rabbit or the variations observed in a rabbit with low blood pressure resulting from the withdrawal of blood.

Trypan blue injected intravenously localizes and concentrates in a normal rabbit more or less uniformly throughout the area of skin treated with xylol. In some of the rabbits with low blood pressure this dye localizes and concentrates at the periphery of these xylol-treated areas of skin. The reddish-brown color of the xylol-treated areas of skin which is usually present in such animals has been observed in other experiments.[6] At this time we have no information or suggestions as to the mechanism of this phenomenon in which trypan blue localizes and concentrates at the periphery of a reddish-brown zone of xylol-treated skin and not in the center. Vascular occlusions have not been noted in the histologic sections. The rabbit's blood pressure must be very low before there is a significant decrease in the development of the inflammatory reaction as shown by the macroscopic changes in the skin and by the diminution or complete absence of leucocytes in the tissues. Variations in the localization and the concentration of trypan blue may be observed in animals with a pressure somewhat higher than that which is present when leucocytes fail to localize in the area of tissue about the irritants.

It is difficult to maintain the rabbits for several hours with very low blood pressures and many of them die. Clotting occurs in the cannula and makes recording unsatisfactory.

There is one important factor to consider in these studies. Is there a sufficient number of leucocytes in the peripheral blood of these rab-

bits to localize and to concentrate about the bacteria? Thirty cubic centimeters of blood are removed from each of four rabbits and white blood cell counts are made on the blood obtained from the ear of each rabbit at frequent intervals during a period of six hours. This quantity of blood is similar to that removed from other rabbits in these experiments. There is a slight increase in the number of white blood cells above the normal in each of these rabbits. This observation would suggest that the failure of leucocytes to localize about the bacteria may not be due to their complete absence in the circulating blood.

To determine the effect that a decrease in the number of leucocytes may have upon the development of any inflammatory reaction a group of four rabbits is given subcutaneous injections of benzene in olive oil. The white blood cell counts are followed daily and when the number of leucocytes reach 3,000 or less a saline suspension of staphylococci is injected intradermally. The macroscopic reaction in the skin appears to be identical with that in rabbits with a normal number of circulating leucocytes. These observations also appear to support the opinion that the failure of leucocytes to localize and to concentrate about staphylococci in rabbits with low blood pressure may be the result of vascular constriction in the small, cutaneous vessels and not the result of a diminution in the number of leucocytes in the circulation blood.

Low blood pressure in rabbits alters the reactions to irritants in the skin. There is a diminution in the degree of hyperemia and edema about the foci of injected staphylococci and aleuronat and a decrease in the number of polymorphonuclear leucocytes which localize in the tissue around these irritants. In rabbits with very low blood pressure both macroscopic and microscopic changes may fail completely to develop.

Trypan blue injected intravenously localizes in areas of inflammation in the skin of rabbits with low blood pressure in a different manner from what it does in normal rabbits. This dye may fail to localize in areas of inflammation in some of the rabbits with exceedingly low arterial pressures.

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A CONSIDERATION OF THE CONTRAINDICATIONS FOR RADICAL OPERATION IN CANCER OF THE RECTUM

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DUE to the radioresistance of carcinoma of the rectum, it is generally agreed that radical operative removal of the tumor offers the best chance of cure. It therefore follows that the higher the operability rate the greater will be the number of patients given a chance of cure. The factors entering into the determination of the operability rate assume great importance in the mortality rate of the operation as well as in the ultimate survival of the patients operated upon. The operability rate depends primarily on the experience of the surgeon in that his judgment must determine whether the growth can be entirely removed with a reasonable mortality and survival rate. As the operability rate rises, the technical difficulties of the operation increase. The operative mortality rises but the *total* number of patients given several years of health or permanent cure should increase. There consequently is a dividing line where in the opinion of the operating surgeon the growth cannot be removed or the patient could not survive the operation.

It is the purpose of this paper to review our personal experience in the last ten years of the operative treatment of cancer of the rectum as it concerns the contraindications for radical removal of the growth. The group of patients concerned are those entering the hospital for operation, and exclude those seen in consultation. This formula is adopted because many patients were seen in consultation, whom we considered operable or inoperable, who either refused operation or went elsewhere.

In reviewing our material from 1930 to August, 1941 we found that we had admitted to the Presbyterian Hospital, for operation, 277 cases of carcinoma of the rectum. Of these we considered five inoperable, one due to vaginal metastases and four because of firm fixation to the sacrum and prostate. The remaining 272 patients were operated upon. Of these remaining 272 cases, 179 were radically operated upon (66 per cent). Of these 179 having removal of the tumor, 105, or 55 per cent, were doubtfully operable due to age (38 over 65 years of age); one or two doubtful nodules in the liver, 15; dense pelvic adhesions, 9; obesity, 10; necessity of resection of the bladder, ureter, prostate, rectovaginal septum, urethra, or adnexa, 18, with the tumor, as well as to other factors not so easily classifiable.

In view of the extension of the indications for radical operation it is obvious that the mortality rate should be kept within a reasonable figure and that the long survival rate after operation should justify the radi-

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cal procedure. Of the 179 patients having removal of the tumor, the hospital mortality rate was 7.2 per cent. The operations performed were one-stage abdominoperineal resections of the rectum in 129 patients with 10 per cent hospital mortality, 28 two-stage Mummery operations, 16 two-stage obstruction resection operations, and when the tumor was at the rectosigmoid junction 5 local removals of small tumors and one resection of the retroperitoneal rectum, all the latter groups with no mortality. During the past ten years we have become increasingly convinced that the one-stage abdominoperineal operation is the operation of choice in most patients. For instance, since 1935 we have done a one-stage abdominoperineal operation 114 times to 5 two-stage Mummery operations during the same period.

A report on the ultimate survival of the patients will be the subject of another communication but our impression is that the extension of operative indications to include cases of doubtful operability is fully justified by the survival rate.

In 93 (34 per cent) patients of the 272 operated upon, the growth was considered inoperable for the following principal reasons:

Extensive liver metastases	40
Infiltration of the growth into the base of the bladder	28
Marked infiltration of the growth into the prostate, vagina or sacrum	25

Table I gives all the causes of inoperability in 98 patients.

TABLE I

CAUSES OF INOPERABILITY IN 98 PATIENTS OF 277 OPERATED UPON

1. Extensive liver metastases	40
2. Infiltration of the tumor into the base of the bladder	28
3. Marked infiltration of the tumor into the prostate, vagina, or sacrum.	23
4. Perforation of the tumor into the soft parts	3
5. Eighty or more years of age and bronchitis or bronchiectasis	1
6. Extensive peritoneal involvement	2
7. Attachment to the posterior abdominal wall	1
8. Large glands along the aorta	1
Total (one patient had more than one cause)	99

Colostomy was performed in 89 of these inoperable patients, with an operative mortality of two (2.3 per cent). The incision was closed in nine patients without doing anything because it was felt that death would ensue before obstruction of the bowel from the tumor would occur. These patients had extensive involvement of the liver, and small tumors causing few symptoms.

We have considered definite liver involvement with metastatic cancer as a contraindication to radical removal of the primary growth in the rectum. There were forty patients or 42 per cent of the whole inoperable group in this category. When, however, one or two small nodules were palpated in the liver, the liver was sandy, or there was any doubt

as to the character of the nodules in the liver, radical operation was carried out. This principle is particularly important because the differential diagnosis between angiomas or adenomas of the liver and early carcinomatous lesions is extremely difficult to make and especially so when the only method available is the sense of touch. We are aware of the fact that several experienced surgeons have advocated radical removal of the cancerous rectum when definite but early involvement of the liver was present. In view of the tedious convalescence following radical removal of the rectum and the short life expectancy (ten months in our cases) where definite liver involvement is found at the operation, we have not considered such a course a sound one. On the other hand, colostomy has been omitted in a number of patients with advanced cancer of the liver and a small rectal growth where it was felt that death from the liver involvement would occur before obstruction took place. Some of these patients have died of intercurrent disease without becoming aware of the hopelessness of their condition. Naturally, this latter group is a small one and is mentioned only to emphasize the importance of individualization in the cases of this inoperable group.

The second largest cause of inoperability is infiltration of the tumor into the base of the bladder. There were 28 cases, or 29 per cent of the whole inoperable group, in this class. This is a very distressing group due not only to their inevitable suffering from a progressive infiltration and often a final rupture into the bladder but also to their tendency to live on an average of fifteen months after the exploratory operation. In the earlier cases we used radium treatment by inserting radium into the growth from the rectal side or by the additional use of radium packs. There is no question that the rate of growth of the tumor is lessened but there is also but little doubt that the patients' suffering is increased. One patient given very extensive radiation lived for three years but it hardly seemed worthwhile in view of the suffering entailed. No patient was cured by radium and it seemed very probable that perforation into the bladder was hastened in some.

In contrast to infiltration of the dome or posterior surface of the bladder where resection of the bladder with the tumor is always carried out, we have adopted a rather hopeless view in the cases having infiltration of the base of the bladder and have not attempted resection. This may be an incorrect decision, particularly in otherwise favorable risks, and perhaps attempts should be made in a small series of cases to resect the base of the bladder and transplant the ureters into the dome of the bladder. Reckless surgery is bad surgery but in this group we are faced with 100 per cent mortality, with a relatively long life expectancy if no attempt at removal is made. It is therefore reasonable to consider the possibility of extension of the indications for radical operation in a small group of otherwise favorable risks.

There were 23 cases deemed inoperable because of advanced infiltration and fixation of the tumor to the prostate, sacrum, or rectovaginal septum. As already indicated, 5 of these patients were not operated upon at all due to the short life expectancy and most of the others were given a colostomy because of approaching obstruction and marked infection of the tumor. These patients lived on an average of eleven months after operation and were a most distressing group, requiring increasing doses of sedatives. The border line between inoperable fixation and operability where a large part of the prostate or rectovaginal septum is removed with the tumor is not easy to define. We have increased gradually the indications for operation in that group and in the period under discussion have removed a part of the prostate, urethra, or rectovaginal septum in thirteen patients. There were two postoperative deaths but otherwise we are in favor of the procedure. We have also removed a part of the sacrum in a few patients but we have not felt encouraged to continue doing so.

Perforation of the tumor into the soft parts or with abscess formation was a contraindication for operation in three patients. This complication is not a frequent one and is not an absolute bar to radical removal of the tumor if it is possible to include the soft parts in the resected specimen.

Two patients had rather extensive peritoneal involvement with carcinoma, which made radical operation inadvisable but the presence of peritoneal plaques of carcinoma around the intraperitoneal tumor has not deterred us from radical operation. The prognosis in that group will, of course, be considerably clouded.

During this period we have considered age alone as contraindication for radical operation in only one patient, a man 81 years of age with a marked bronchitis. Thirty-eight patients over 65 years of age have had surgical removal of their tumor and while the operative mortality (four deaths) from pneumonia and embolism is higher in this group than in a younger age group, the survival rate justifies the procedure. The type of operation used in this age group must be selected carefully.

The size of the tumor has relatively little to do with its operability. Small tumors may have extensive metastases into the glands or liver and large tumors may have none. The only disturbing factor in large tumors is the mechanical one and we favor the one-stage abdominoperineal operation exclusively in that group.

Enlargement of the lymphatic glands along the superior hemorrhoidal and inferior mesenteric vessels or even along the aorta is not considered a contraindication to operation because many such glandular enlargements are due to infection and we have found from a careful study of these glands that it is not possible to be sure of the nature of the enlargement without histologic examination. Where glands are grossly enlarged it is wise to extend the upper limits of the operation as far

as possible, ligating the superior mesenteric artery just distal to the first sigmoid branch and in some instances carrying dissection of the soft parts above the ligation.

Attachment of the intraperitoneal portion of the tumor to the uterus or adnexa, dome of the bladder, ureter or other loops of bowel should not be a contraindication to radical operation as these structures can be removed with the tumor.

Adiposity is no contraindication per se for radical operation although it must be said that the technical difficulties of the operation are increased from the standpoint of exposure and control of hemorrhage and that postoperative complications such as disruption of the wound, infection of the wound, and cardiovascular unbalance are more to be anticipated. One patient died postoperatively in this group but no patient was refused operation because of adiposity.

Diabetes, cardiovascular disease, anemia, avitaminosis, low serum protein, dehydration, and partial obstruction of the bowel are all treated medically in the preparatory stage admitting all cases a week before the operation. If the obstruction of the bowel cannot be taken care of medically by diet, large enemas, and mild saline laxatives, a preliminary colostomy is done. This is necessary in a relatively small number of cases.

SUMMARY

Of 277 patients coming to the hospital for operation for cancer of the rectum, 98 were considered inoperable. Of these, 84 were colostomized.

The contraindications for removal of the tumor were liver metastases in 40, attachment to the base of the bladder in 28, and infiltrative attachment to the sacrum, prostate, or rectovaginal septum in 23.

Adiposity, age, cardiovascular disease, large tumors, enlargement of regional lymph glands, resectable attachment of the tumor to the prostate, rectovaginal septum, uterus, or adnexa, dome of the bladder or ureter are not considered contraindications to radical removal of the tumor.

The decision to extend the indications for radical operation in cancer of the rectum so that 65 per cent of the patients coming to the hospital for operation may be given the benefit of curative operation will increase the operative mortality but will result in an actually larger number of patients being given a long-term cure.

Editorial

Contamination of the Peritoneum

CONCURRENT with widening possibilities in the prevention and control of surgical infections through recent developments in chemotherapy, the distinction between contamination and infection of wounds is receiving the attention it deserves. Curiously enough, few observers have made the same distinction in regard to the peritoneum in association with disease, particularly appendicitis. That the distinction is valid in the peritoneum, as elsewhere, is indicated by established surgical principles under conditions in which the contaminating organisms are less virulent and less numerous than in appendicitis, as in perforation of a duodenal ulcer. It is widely recognized that the peritoneum, although contaminated, may escape infection if the source of contamination is promptly eliminated. During operation on a perforated duodenal ulcer one often sees gross changes which are compatible with peritonitis, that is, injection, dulling, fibrin deposits, and free fluid, even a short time after the contamination has occurred. That these appearances are not necessarily evidences of established peritoneal infection is quite clear from the subsequent course of the disease. What they represent, in fact, is an inflammatory process in response to contamination and chemical damage, resulting in destruction of invading organisms. The histologic picture of a contaminated wound which is successfully handling contamination differs from the histologic appearance of this inflammatory process in the peritoneum only through the differing natures of the tissues involved.

It is quite obvious that mere inspection of, or even positive culture from, the peritoneal surfaces, after contamination from a perforated duodenal ulcer, does not indicate whether or not a definitely established infection of the peritoneum will eventuate. The same is true of the appearances in the neighborhood of a recently perforated appendix. Yet almost all authors classify as peritonitis any perforation of the appendix which shows an inflammatory process in the neighboring peritoneum. As was pointed out by Lehman and Parker,[1] among others, many of these early perforations are no more than contaminations of the peritoneum and do not present the real problems of an established peritonitis if the source of the contamination is promptly removed. Just as in accidental wounds, only the subsequent course of the disease will indicate whether or not peritonitis has occurred.

The unmistakable fact of perforation of the appendix has too long governed the classification of the complications of appendicitis. Although contamination of the peritoneum must obviously precede infection, yet it does not necessarily establish the occurrence of the more serious complication.

Any statistical study which groups all perforations of the appendix under the head of Peritonitis is presenting a distorted picture of the latter. The effect of this type of classification is to improve tremendously the mortality rate of peritonitis inasmuch as that group then contains a large percentage of cases which have actually never been true peritonitis. The cases of contaminated peritoneum can justly be included, after the postoperative course is known, in the group of uncomplicated appendicitis, as was done by Lehman and Parker. Inasmuch as, by definition, all these cases recover (with the exception of rare deaths from complications unrelated to the intra-abdominal disease) this procedure does not alter the mortality rate for the simple group. On the other hand, by excluding the contaminated peritoneum, it definitely presents a more accurate picture of true peritonitis. A second method of handling this group is one illustrated by Penberthy's recent paper,[2] in which, however, he still uses the term peritonitis. In his group of "acute unruptured appendicitis" the mortality is .44 per cent. It is noteworthy that the mortality of the group of "acute ruptured local peritonitis" is approximately the same as that of simple appendicitis, namely .55 per cent. This clearly indicates that this latter group is not peritonitis but presents only the contaminated peritoneum. Lehman and Parker in a series of cases of all ages reported a high mortality, namely 40.6 per cent, in their group of true peritonitis, whereas Penberthy's mortality in infants and children was as high as 64.9 per cent. (In both series localized peritonitis represented by an inflammatory mass or an abscess was properly reported as a separate problem.) These mortality figures for peritonitis are probably more nearly the correct figures than are those coming from clinics in which the number of cases of true peritonitis is diluted by a large percentage of cases of contaminated peritoneum. This effect is illustrated by combining Penberthy's groups of "acute ruptured local peritonitis" and "acute ruptured diffuse peritonitis," a procedure that results in a mortality of 22.3 per cent for peritonitis from perforated appendicitis. Such a figure more nearly approaches the usual mortality reported.

The importance of this distinction in relation to appendicitis is emphasized at the present time by a large number of reports dealing with sulfonamide treatment of peritonitis. Tashiro, Pratt, Kobayashi, and Kawaichi[3] report twenty-three cases of peritonitis from acute appendicitis treated by sulfanilamide intraperitoneally. Of these twenty-three cases, nine were operated upon within twenty-four hours of onset. These nine cases, nearly one-half, are not necessarily cases of peritonitis at

all. Certainly most of them would have had an equally smooth course without the use of the drug.

Such comments are not meant to imply any disapproval of the local use of the sulfonamides in cases of contamination of the peritoneum. According to our present knowledge of their effectiveness it is probable that in these cases their use is most justified and presents the best promise of utility.

The real problem is to obtain a true statistical picture of the results of the treatment of true peritonitis, a highly fatal disease, the control of which is far from satisfactory with or without chemotherapy. There is no possibility of judging how effective the sulfonamides or any other treatment may be in true peritonitis so long as cases of contaminated peritoneum are permitted to fog the results. It is urged that the distinction between contamination and infection, now so well established in surgical thought in dealing with other tissues, be kept in mind when dealing with the peritoneum in connection with appendicitis. An inflammatory process of the peritoneum representing the defense mechanism against contamination is by no means, necessarily, in practical effect an established peritonitis with the difficult clinical problems presented by that disease.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

MENINGOCEREBRAL ADHESIONS

AN EXPERIMENTAL STUDY OF THE EFFECT OF HUMAN AMNIOTIC MEMBRANE, AMNIOPLASTIN, BEEF ALLANTOIC MEMBRANE, CARGILE MEMBRANE, TANTALUM FOIL, AND POLYVINYL ALCOHOL FILMS

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INTRODUCTION

IN THE World War of 1914-1918 the treatment of craniocerebral injuries was steadily improved. The passage of each year brought the adoption of new surgical principles directed not only toward the lowering of the mortality rate but, in addition, the prevention of early and late complications. Many of these early deaths were on the basis of infection, a complication which will be largely overcome in the present emergency by the judicious use of chemotherapy. The late complications have been the problems of the postwar years, namely, paralytic phenomena, disorders of speech, mental disturbances and post-traumatic epilepsy. This study was undertaken with a view to the better management of this last-named complication.

Penfield[51, 53, 54] has repeatedly emphasized the importance of the meningeal ingrowth of the cerebral wound in the production of convulsive phenomena. In contradistinction to the past theories which stressed the importance of the mechanical pull on the brain alone, he believes that the responsible element in rendering the scar epileptogenic is the establishment of a crossed circulation with the overlying tissues. This leads ultimately to destruction and revascularization of the cerebral cortex. In 1930, he collaborated with Foerster[22] in a study of twelve cases of post-traumatic epilepsy. In a few of these patients seizures were induced on the operating table by tugging on the dura overlying a meningocerebral cicatrix. On the basis of these observations they suggested that a vasomotor reflex secondary to traction may be responsible for the initiation of seizures.

As further evidence for the importance of meningeal ingrowth, Penfield[51] has pointed out the higher incidence of convulsive seizures following head injuries with, as compared to those without, dural penetration. Rawling[56] analyzed 452 cases of head injury sustained in World

War I and found the incidence of seizures following craniocerebral wounds of various types to be as follows: penetrating wound with hernia, 54 per cent; penetrating wound, 35 per cent; penetrating wound with foreign bodies retained, 33 per cent; perforating wound, 16 per cent; fractured base, 14 per cent; nonpenetrating wound, 13 per cent; scalp wounds, 10 per cent.

Wagstaffe,[70] in a study of 377 cases of gunshot wound of the head, noted a seizure incidence of 18.7 per cent in wounds with dural penetration and less than 2 per cent in those cases where the dura was not penetrated. The statistics of Stern, quoted by Schou,[67] are 20 to 50 per cent for open craniocerebral injury and 2 to 4 per cent for closed injury.

These observations, however, are not acceptable as evidence in favor of the importance of meningocerebral adhesions alone in the causation of seizures. Although the formation of adhesions would be greater in the cases with dural penetration, the destruction of nervous tissue would also be greater under these circumstances. Furthermore, it is likely that many of the nonpenetrating injuries were confined to the superficial structures and did not involve the underlying brain.

A third point of evidence in favor of the importance of meningeal ingrowth is Penfield's[51] observation of the greater frequency of seizures in meningocerebral, as compared to cerebral, cicatrix. He believes that the incidence must be much lower in the cerebral cicatrix where there is little or no admixture of connective tissue. In support of this contention he points out the infrequency of seizures in patients with cerebral scars resulting from vascular occlusion.

This study is based on the theory that meningeal invasion is an important factor in determining the epileptogenic nature of a cerebral wound. The importance of the work is modified, therefore, by the acceptance or rejection of the adhesion hypothesis. However, this hypothesis will not be established as factual until a proved method of adhesion prevention is used in the surgical treatment of craniocerebral wounds and is followed in later years by a study of the incidence of post-traumatic epilepsy in cases so treated.

Our study is principally a continuation of the work of Chao, Humphreys, and Penfield[12] on the prevention of meningocerebral adhesions with amnioplastin, a membrane prepared from the human amnion. In addition, other materials including Cargile membrane, allantoic (insultoic) membrane, films of polyvinyl alcohol, and tantalum foil have been tried. Although an ideal material has not been found, the study has disclosed certain facts which must be considered in the use of these substances and, more important, in the final solution of the problem.

REVIEW OF THE LITERATURE

The problems involved in the prevention of meningocerebral adhesions have been approached in two directions, by reviewing (1) the factors

involved in the evolution of the meningocerebral scar, and (2) the methods which have been used in the past for this purpose.

The Formation of the Meningocerebral Cicatrix

Adherence to overlying structures is not the invariable component of cerebral injury. Any lesion, whether of a vascular, inflammatory or traumatic nature, which does not disturb continuity of the arachnoid, is not followed by adhesions. Our knowledge of this protective role of the arachnoid is due to the investigations of Harvey and his associates.

In 1923, Sayad and Harvey[64] published their observations on the reactions of the meninges to injury. They performed the first series of experiments on dogs. Discs of dura mater were excised leaving the leptomeninges uninjured. The dural defect was rapidly obliterated with blood clot, having only fibrinous attachments to the arachnoid. Within one week the arachnoidal surface of the clot was carpeted with a thin layer of endothelial cells and the fibrinous attachment to the arachnoid disappeared. They therefore concluded that the dura mater will regenerate without adhering to the intact arachnoid.

In the following year Lear and Harvey[38] reported their studies on the regeneration of the injured pia-arachnoid of dogs. To ensure the intactness of the overlying dura they reflected it from the cortical surface in the form of a large flap. The leptomeninges lying directly beneath the center of the dural flap were injured with either a blunt instrument or the electrocautery. Dural adhesions occurred in all instances. This led them to postulate that, in the repair of the leptomeninges, the dura mater does not serve as a limiting membrane but enters actively into the healing process.

The studies of Penfield[49, 50] and Rio-Hortega and Penfield[60] have been valuable contributions to the pathogenesis of the meningocerebral cicatrix. They studied the sequence of events from within a few hours of the injury to the formation of the mature scar.

Within six hours of the injury the traumatic defect in the brain is filled with blood clot. The intensity of the fibroblastic-glial reaction which then ensues is directly proportional to the amount of remaining devitalized cerebral tissue. Within twenty-four hours the neighboring microglia develop an ameboid form and start their migration toward the site of injury. At the end of the second day they are compound granular corpuscles and are actively phagocytizing debris. This phagocytosis continues until all of the unnecessary materials have been removed. It is not uncommon to find these cells, filled with products of destruction, within the interstices of the scar many years after the injury. Penfield[53] describes one case in which fat-filled phagocytes were found in the border of a twenty-eight-year-old scar.

The astrocytes also play an important role in the repair process. At the end of the first day the astrocytes in the immediate neighborhood of

the wound have undergone clasmatodendrosis. Those in the more distant zone show swelling, without fragmentation, of both cell body and processes. On the fourth day these swollen cells undergo amitotic division and begin to lay down fibrils at the margin of the wound. By this time fibroblasts from the overlying dura muscle, and blood vessels have permeated the clot and are soon intimately blended with the neuroglia fibrils of the wound edge. Blood vessels proliferate and penetrate the fibroblastic-glial meshwork and eventually form a rich anastomosis with the cerebral vessels.

The final stage is one of contraction of the connective tissue core. This pull is transmitted to the glial fibrils causing them to be orientated perpendicularly to the surface of the cerebral wound. At times this traction is so great that the sucker feet of astrocytes are displaced through the pia mater. A further indication of the pull is the migration of the lateral ventricle toward the site of the lesion.

In summary, therefore, there are two factors which influence the formation of the meningocerebral cicatrix. Most important is the damage to the arachnoid which predisposes the connective tissue invasion from the overlying structures. The second factor is the extent of brain destruction, the density of the resulting scar being directly proportional to the volume of devitalized tissue.

The Prevention of Meningocerebral Adhesions

The observations on methods and materials employed to prevent adhesions between the wounded brain and its enveloping structures are but few when compared to the voluminous literature on adhesion prevention in the other serous spaces of the organism. Especially impressive is the array of methods and materials used to prevent postoperative peritoneal adhesions. These are listed and discussed in the extensive reviews of Richardson[59] and Ochsner and Garside.[47] The size of this list is testimony to the difficulties presented in the solution of the problem. Similar difficulties exist in the prevention of adhesions in joint spaces and around sutured nerves and tendons.

In past years more attention has been focused on methods for the repair of dural defects than on the prevention of meningocerebral adhesions. The materials and techniques for duraplasty have been reviewed by von Saar,[69] Buné,[6] de Bernardis,[15] Caporale and de Bernardis,[11] and Glaser and Thienes.[25] These experiments have been of great interest and value in the present study. The reaction of the surrounding tissues to these materials, especially when the arachnoidal barrier is broken, has served as a guide in the selection of materials for this investigation. For purposes of review and discussion the materials used in the past for either duraplasty or the prevention of meningocerebral adhesions may be classified as (1) metals, (2) viable animal membranes, (3) nonviable animal membranes, (4) miscellaneous materials.

Metals.—The debut of the modern period in the surgery of post-traumatic epilepsy, which was pioneered by Horsley in the latter part of the nineteenth century, was followed by the first reports on the use of materials to prevent meningocerebral adhesions. Horsley excised the epileptogenic cicatrices but did not cover the area of removal with protective materials. Beach is credited with the first suggestion to use these substances. In 1890, he[3] described a case of post-traumatic epilepsy treated by lysis of the meningocerebral adhesions. At this time he stated that should the seizures recur he would reoperate and implant gold foil between the brain and dura. In 1897, he[4] reported that this plan was effected at a secondary craniotomy in 1892. The patient's attacks recurred, but with diminished frequency and intensity. The condition of the foil was not mentioned.

The popularity of the metallic foils in the surgery of epilepsy was maintained well into the first decade of the twentieth century. The observations of Beach on gold foil were followed by the reports of Oliver,[48] Estes,[19] Summers,[68] and Woolsey[71] on this metal, those of Ray,[57] Harris,[29] and Prime[55] on silver foil, and Morehead,[44] and McCosh[42, 43] on platinum foil. Chao, Humphreys, and Penfield[12] have recently reported their experiences with silver foil, aluminum foil, nickel plate, and stainless steel plate.

One feature common to all of these metals is encapsulation. The thickness of the capsule and the intensity of the cellular reaction have been variable. Both would seem dependent on the extent and character of the corrosion of the metal. The good clinical results obtained in some cases are overshadowed by the finding of dense adhesions between the brain and dura in all instances where direct observations on the condition of the metals were made.

Viable Animal Membranes.—At the close of the first decade of the twentieth century the metallic substances were being discarded in favor of viable and nonviable animal membranes. The viable membranes have generally been employed for the closure of dural defects and not for the prevention of meningocerebral adhesions. This work originated in 1909 when Kirschner[34, 35] used autoplastic fascia lata for dural restoration in dogs. The first human duraplastic operation with fascia lata was performed by Körte,[36] in 1910. A variety of viable membranes have since been employed. Among the autoplastic tissues are dura,[5] periosteum,[6, 63] and fat.[12, 16, 58] Homoplastic hernia sac was successfully used in man by Finsterer.[20, 21] Burger[8] attempted to replace the dura mater in cats with fresh, human amniotic membrane obtained at cesarean section but his results were inconclusive. Chao, Humphreys, and Penfield[12] present the only experimental data on the specific use of viable membranes to prevent meningocerebral adhesions. Both fat and fascia lata were used over brain wounds in cats. Adhesions occurred in all of the experiments.

An analysis of the results obtained by these observers allows certain conclusions to be drawn. From the standpoint of dural repair the autoplastic, viable membranes have been uniformly successful. However, if the cerebral cortex was damaged meningocerebral adhesions occurred.

Nonviable Animal Membranes.—A large number of materials classifiable in this category have been employed over the intact and damaged cerebral cortex. In 1898, Freeman[23] described two experiments, one on a dog and the other on a rabbit, in which the vitelline membrane of the hen's egg was placed over the wounded brain. The experiment on the dog was inconclusive due to suppuration of the wound. At the end of two months the brain of the rabbit was yellow at the site of the wound but was smooth and nonadherent except by a few trivial and delicate adhesions around the edge of the dural opening. Greer[26] and Prime[55] subsequently reported their observations on this membrane. Prime noted adhesions in every instance if the cortex was damaged.

Other nonviable animal membranes which have been investigated are Cargile membrane,[12, 13, 55] prepared hernia sac,[20, 21, 69] human amniotic membrane,[12] beef allantoic membrane,[12] catgut membrane,[11, 12, 15] sheep peritoneum,[27] and calf artery.[61]

These nonviable membranes have shown the greatest promise in the prevention of meningocerebral adhesions. This is especially true of amniotic and allantoic membranes. While both materials provoke a foreign body reaction and are eventually encapsulated, the reaction has been comparatively minimal. Adhesions have been trivial or absent in a large number of the experiments. Caporale and de Bernardis[11] describe excellent results with catgut membrane. In their experiments on rabbits the membrane was adherent to the brain wound but not to the overlying structures. However, their good results were not confirmed in the experiments of Chao and his colleagues.[12]

Miscellaneous Membranes.—Various substances of plant or mineral origin are included in this group, namely celluloid,[28] parchment,[46] mica and cellophane,[12] olive oil,[55] and rubber tissue.[1] The experience with these materials has been generally unsatisfactory. With but few exceptions dense encapsulation and adhesion formation have been found at a later date.

THE SELECTION OF MATERIALS

An analysis of the results obtained with the aforementioned materials has been invaluable in the selection of substances for the present study. We have subjected a few of the more promising materials to further investigation. Other materials have been selected on the basis of the following characteristics:

1. Inertness. Provocation of minimal reaction in the surrounding tissues. This is the most important requirement.

2. Delayed resorption. The material should remain intact and check the ingrowth of fibrous tissue from the overlying structures throughout the period required for complete bridging of the cerebral wound by the arachnoid.

3. Availability of supply.

4. Ease of sterilization.

While an ideal membrane should possess all of these qualities, resorption would be dispensable if the material remained permanently inert in the tissues.

The materials used in this investigation may be classified as both resorbable and nonresorbable. They include, (1) amniotic membrane, in fresh, attenuated and fixed (amnioplastin) forms; (2) allantoic (insultoic) membrane; (3) Cargile membrane; (4) tantalum foil; (5) polymerized vinyl alcohol films.

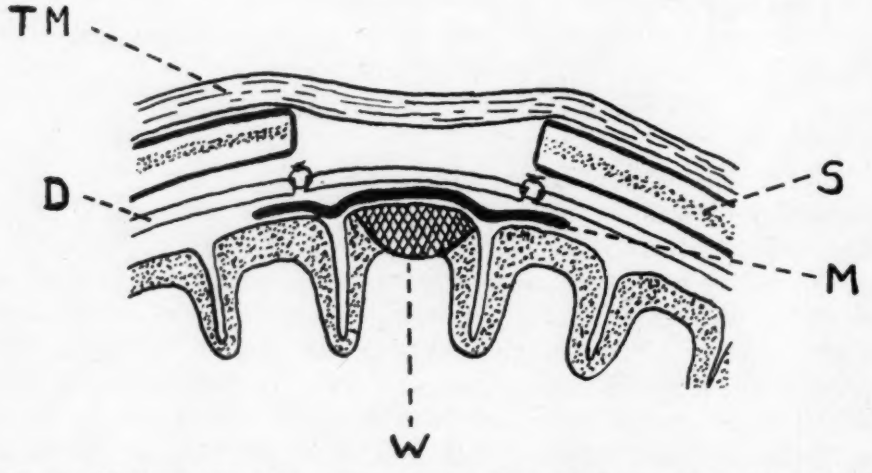

Fig. 1.—Diagrammatic cross section showing the method of covering the cerebral wound (*W*) with the membrane (*M*). Temporal muscle (*T. M.*); dura (*D*); skull (*S*).

EXPERIMENTAL DATA

A total of seventy-six cats was used during this study. All operations were carried out under rigid aseptic precautions. Bilateral openings in the skull, 1.5 to 2.0 cm. in diameter, were made in the parietal regions. The dura was incised about 2 mm. from the anterior, medial, and posterior margins of the bony defect and reflected laterally in the form of a flap. Wounding of the cerebral cortex was accomplished by electrocoagulation of the surface of one or more gyri. The area of thermal destruction was then pierced several times with the point of a scalpel. In some instances only one side of the brain was wounded. Both the wounded and unwounded cerebral hemispheres were covered with the material of choice and the borders were tucked well under the cut edges of the overlying dura (Fig. 1). The dura was closed with two

fine silk sutures. The temporal muscles, galea and skin were apposed with interrupted sutures of black silk.

The animals were killed at appropriate intervals varying from 4 to 240 days. Painstaking care was exercised in the removal of the brains. Prior to removal they were fixed in situ by the injection of 10 per cent formalin into both internal carotid arteries. The removed brain, well covered with dura over both the base and convexity, was placed in 10 per cent formalin until ready for gross section. When properly fixed it was sectioned in the coronal plane. One section was designed to pass through the center of the cerebral wounds (Fig. 2). The posterior block resulting from this section was examined grossly for adhesions. The anterior block was embedded in paraffin for microscopic study. To avoid distortion of the tissue relationships during the washing, dehydrating, clearing, and paraffin embedding processes, the dura was fastened to the brain and leptomeninges with black silk sutures. Sections for the histologic study were cut at a thickness 8 to 10 μ and stained with the hematoxylin and van Gieson, the Mallory phosphotungstic acid hematoxylin and the Mallory aniline blue methods.

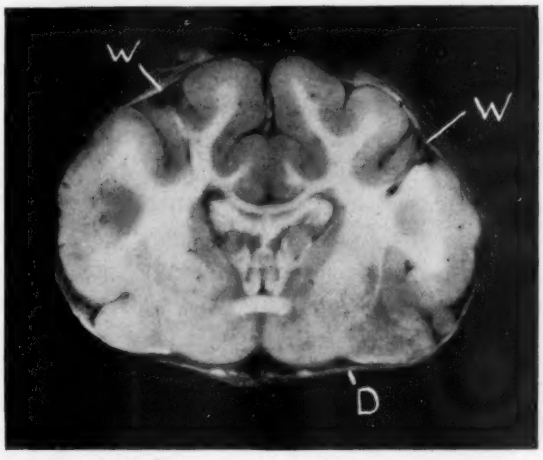

Fig. 2.—Coronal section of the brain showing the wounds (*W*) in both cerebral hemispheres; the dura (*D*) is intact over the convexity and base.

Amniotic Membrane

Historical Survey.—In 1911, Schmerz[65] published a report of the first known attempt to use amniotic membrane for the prevention of adhesions between serous surfaces. He used a formalinized human amniotic membrane with success in the treatment of disabling adhesions in three patients with gunshot wounds involving their tendon sheaths and a fourth case of ankylosis of the elbow. It is interesting that in this report he mentions the possible value of amniotic membrane in myolysis, neurolysis, and duraplasty. In a later communication[66] he described the successful recovery of function in a case of ankylosis of the knee joint treated by interposition of this material.

Lyman and Bergtold[40] used human amniotic membrane to prevent postoperative peritoneal adhesions in seven human cases. While they reported success, their conclusions were drawn entirely on clinical observation.

The successful use of amniotic membrane reported in these earlier papers apparently aroused but little enthusiasm. No further observations on this material are recorded until 1933, at which time Lyons[41] reported the satisfactory epithelization of two postoperative mastoid cavities lined with fresh, sterile human amniotic membrane obtained at cesarean section. In 1937, Johnson[31] reported good results with human amniotic membrane in avoiding adhesions between the traumatized peritoneal surfaces of rabbits. However, he noted[32] that the membrane was treated as a foreign body by the contiguous tissues. In the same year Davis and Aries[14] reported their observations on beef and human amniotic membranes used for the prevention of adhesions around repaired nerves and tendons and between the denuded peritoneal surfaces of dogs. The nerve and tendon experiments were unsuccessful but excellent results were obtained in the peritoneal cavity.

Burger[8] has described three cases of successful reconstruction of the human vagina with fresh fetal membranes obtained at cesarean section. He and his associates have also used living human fetal membranes to replace the dura in cats. He notes, "In one of the cases the adherence was satisfactory, still this lone case was not sufficient for the solution of our problem."

The first observations on the use of amniotic membrane to prevent adhesions between the brain and its coverings were those reported by Chao, Humphreys, and Penfield.[12] These workers reported success with amnioplastin, a specially prepared form of human amniotic membrane. The membrane was placed over the wounded cerebral cortex and leptomeninges of cats. The animals were killed at regular intervals up to sixty days. The membrane caused only a slight cellular reaction and was completely absorbed at the end of thirty days. Within this thirty-day period the pia-arachnoid had covered the cerebral wound, and adhesions to the overlying structures did not occur. Their consistently good results led these observers to recommend amnioplastin "as a preventative of meningocerebral adhesions and as an adjunct to radical surgery necessary to prevent post-traumatic and postoperative epilepsy."

In a later communication Penfield[52] warned against use of amnioplastin until further studies had been carried out. This warning was issued principally because of his knowledge of the unsatisfactory results obtained by us with amnioplastin up to that time. The second factor was the unfavorable postoperative course in a case of focal epilepsy treated by covering the area of scar excision with amnioplastin. At the second craniotomy seven months later, dense connective tissue had bound the brain to the dura.

Recently several enthusiastic reports on the clinical use of amnioplastin have appeared in the literature. Garcin and Guillaume[24] have used it to repair dural defects associated with craniocerebral gunshot wounds. Rogers[62] favors the use of this membrane following craniotomy and neurolysis. He records no observation on the tissue reaction to the membrane. Law and Philip[37] and de Rötth[17] report that amnioplastin and human fetal membranes are of value in ophthalmologic surgery.

Methods and Materials.—In the earlier experiments human amniotic membrane was prepared in the manner outlined by Chao, Humphreys, and Penfield.[12] This requires the separation of the amnion from the chorion by finger dissection, washing in running water, fixation in 70 per cent alcohol, stretching and drying on a glass plate and finally, sterilizing in the autoclave for twenty minutes at 250° F. with 120 pounds' steam pressure.

Due to our disappointing results with the membranes so prepared, other techniques were used. For practical purposes we have classified the various membranes as fixed, fresh, and attenuated types.

Fixed Amniotic Membrane (Amnioplastin): Human amniotic membrane* obtained at delivery was subjected immediately to one of the following methods of preparation:

1. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; boiled, 20 minutes.

2. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

3. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; boiled, 20 minutes; 70 per cent alcohol, 9 days.

4. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; 70 per cent alcohol, 7 days; boiled, 20 minutes; 70 per cent alcohol, 24 hours.

5. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; 70 per cent alcohol, 15 minutes; boiled, 20 minutes; 70 per cent alcohol, 24 hours.

6. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 24 hours; 70 per cent alcohol, 4 days; boiled, 20 minutes; 70 per cent alcohol, 24 hours.

7. Washed in 70 per cent alcohol, 24 hours; boiled, 20 minutes.

8. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; 4 days in 60° C. oven; ether, 24 hours; boiled, 20 minutes; 70 per cent alcohol, 24 hours.

9. Washed in 70 per cent alcohol, 25 days.

10. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 5 days; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

11. Washed in 70 per cent alcohol, 24 hours; 95 per cent alcohol, 24 hours; absolute alcohol, 24 hours; ether, 5 days; boiled, 20 minutes.

*The fetal membranes were supplied through the generosity of the staff of the Royal Victoria Montreal Maternity Hospital.

12. Washed in 70 per cent alcohol, 1 hour; ether, 5 days; dried, 5 days; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

13. Washed in 70 per cent alcohol, 1 hour; ether, 5 days; dried, 5 days; boiled, 20 minutes.

14. Washed in ether, 6 days; dried; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

15. Washed in ether, 6 days; dried; boiled, 20 minutes.

16. Washed in ether, 4 days; 70 per cent alcohol, 10 minutes; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

17. Washed in ether, 4 days; 70 per cent alcohol, 10 minutes; boiled, 20 minutes.

18. Washed in 70 per cent alcohol, 10 minutes; ether, 5 days; 70 per cent alcohol, 20 minutes; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

19. Washed in 70 per cent alcohol, 10 minutes; ether, 5 days; 70 per cent alcohol, 20 minutes; boiled, 20 minutes.

20. Washed in 70 per cent alcohol, 20 minutes; ether, 9 days; 70 per cent alcohol, 5 minutes; dried, 4 days; autoclaved 20 minutes at 250° F., with 120 pounds' pressure.

21. Washed in 70 per cent alcohol, 20 minutes; ether, 9 days; 70 per cent alcohol, 5 minutes; dried, 4 days; boiled, 20 minutes.

22. As outlined by LeVann.[39] Amnion separated from chorion, placed in acetone 15 hours, rinsed in 70 per cent alcohol, dried on rough toweling 24 hours, then immersed in ether 12 hours, rinsed in 70 per cent alcohol, dried 24 hours and sterilized in the autoclave.

Fresh Amniotic Membrane: The membranes were obtained at cesarean section, placed immediately in a sterile container, and kept in an incubator at 37° C. until ready for use. At the time of operation the amnion was separated from chorion by finger dissection, cut to the desired size, and placed on the brain. The time between cesarean section and implantation did not exceed three hours.

Attenuated Amniotic Membrane: Selected pieces of the fresh membrane were placed in sterilized tubes of liquid petrolatum and kept in a refrigerator at 3° C. for approximately one month before use. This is Huber's[30] method for storage of nerve grafts.

Experimental Results.—Without exception, the membranes were treated as foreign bodies by the tissues and enveloped in a connective tissue capsule of varying thickness. In the majority of experiments there was, in addition, a moderate degree of cellular reaction involving small round cells and a few foreign body giant cells. Occasionally this reaction was intense. Although the different methods of preparation did produce some variation in the thickness of the capsule, the cellular reaction, and the rate of resorption of the membrane, they did not appreciably alter the end results. Ultimately the cerebral wound became bound to the overlying dura by a connective tissue core (Fig. 3). Our earlier impression that the fat-free membrane would prevent adhesions proved to be false.

There are several stages in the encapsulation of the fixed membrane. Disintegration of the membrane begins in the epithelial layer and involves the collagen layer at a later period. Shortly after implantation

the epithelial cells become swollen and are eventually broken up into globular, amorphous material. The entire membrane was usually absorbed after thirty to sixty days. However, in several animals traces of it were still present at the end of four months. The membranes prepared in alcohol alone remained intact longer than the other types. Furthermore, the same piece of membrane was usually resorbed more slowly if it had been sterilized by boiling rather than in the autoclave. This would seem due to the shrinkage and thickening of the membrane caused by the boiling.

The connective tissue forming the capsule became adherent earlier to the collagen layer of the membranes. Adherence to the opposite surface was delayed until the epithelial cells had disappeared. Finally, with the onset of resorption of the collagen layer, connective tissue fibers traversed the clefts in the membrane and eventually fused the inner and outer layers of the capsule.

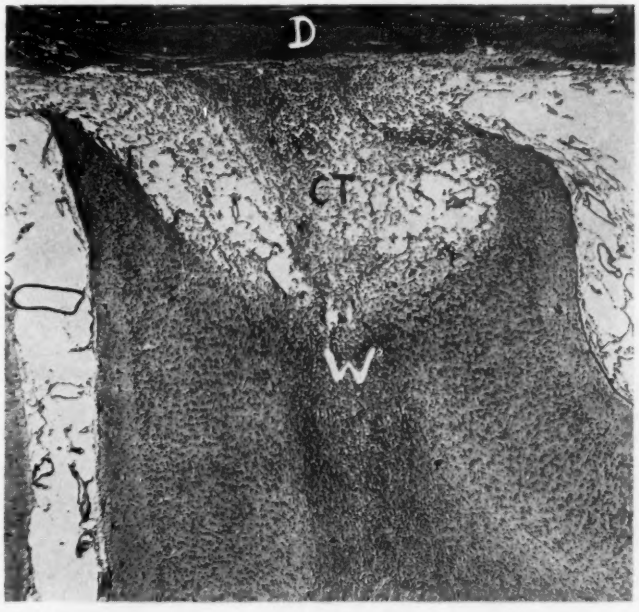

Fig. 3.—Result twenty-eight days after emplacement of amnioplastin; the membrane has disappeared. Dense connective tissue (*CT*) binds the cerebral wound (*W*) to the overlying dura (*D*). Hematoxylin and van Gieson stains.

There were but five encouraging results in the series of ninety-five cerebral wounds covered with amnioplastin. In four of these the animals had only delicate meningocerebral adhesions on gross inspection. In these cases microscopic examination showed the cerebral wound to be partly bridged by the regrowth of pia-arachnoid. This carpet of leptomeningeal cells was interrupted centrally by the meningocerebral band of connective tissue. The one good result occurred in a cat killed after 118 days. In this experiment there were no adhesions on gross inspection. However, microscopic examination dis-

closed a few filamentous strands which may have been broken during the process of removal or fixation.

Uniformly poor results were obtained with the fresh membranes. Both the capsule formation and the cellular reaction were extremely intense (Fig. 4). The dura and brain were tightly adherent through the medium of this capsule. Large aggregations of small round cells with clumps of foreign body giant cells were the principal components of the inflammatory reaction. The most interesting feature observed in these experiments with fresh membrane was the histologic evidence for viability of its collagen layer. Both the collagen fibers and the fibroblast nuclei dispersed among them, stained with a brilliance and distinctness comparable to that of the native connective tissue.

Use of the attenuated membranes likewise failed to prevent meningocerebral adhesions. However, the cellular reaction to this type of amniotic membrane was less than with the fresh and fixed forms. Encapsulation was slight and the reaction of inflammatory cells minimal (Fig. 5). Furthermore, the collagen layer of these membranes behaved like a viable material. It remained well preserved and eventually became incorporated as part of the connective tissue reaction investing it.

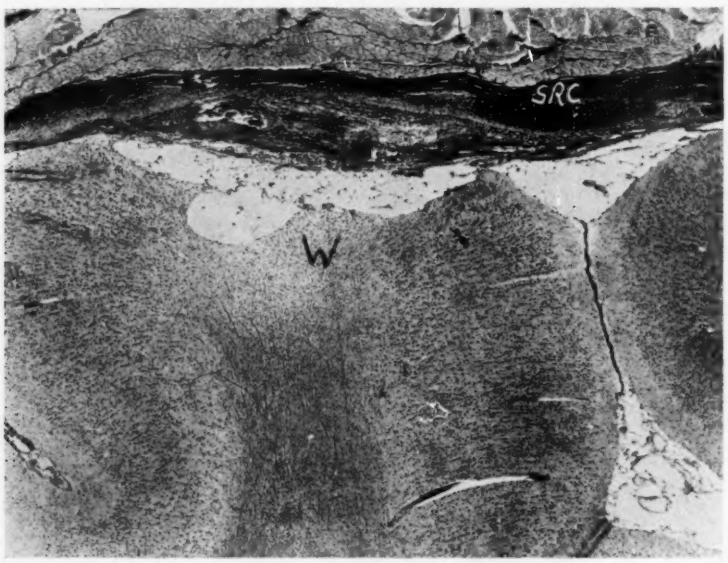

Fig. 4.—Fresh amniotic membrane after ninety-seven days. The capsule is adherent to the cerebral wound (*W*); a large aggregation of small round cells (*SRC*) is shown. Hematoxylin and van Gieson stains.

Allantoic Membrane

Historical Survey.—Beef allantoic membrane, known commercially as insultoic membrane, was first employed for the prevention of adhesions by Johnson.[31] He covered the denuded peritoneal surfaces of rabbits and traumatized tendons of calves with this material. The membrane stimulated a foreign body reaction and was eventually en-

capsulated. Nevertheless, his results were excellent due to the smoothness of the inner surface of the connective tissue capsules. Adhesions did not occur unless the membrane slipped or was of insufficient size to cover the traumatized area.

The excellent results obtained by Johnson have been confirmed by the work of Davis and Aries.[14] These observers covered denuded peritoneal surfaces and the line of suture in nerves and tendons of dogs with allantoic membrane. Around the nerves and tendons this membrane was superior to the control materials, namely, beef and human amniotic membrane, sheet catgut, beef cecum, cellophane, and rubber latex. In the peritoneal cavity, however, better results were obtained with amniotic membrane, especially if its mucous surface was intact. The allantoic membrane prevented peritoneal adhesions only to the extent and size of the patch which was used.

Chao, Humphreys, and Penfield[12] had promising results with allantoic membrane for the prevention of meningocerebral adhesions. The adhesions that formed were few in number and the cellular response slight. In view of their encouraging findings in a small number of experiments, a further study of this membrane seemed warranted.

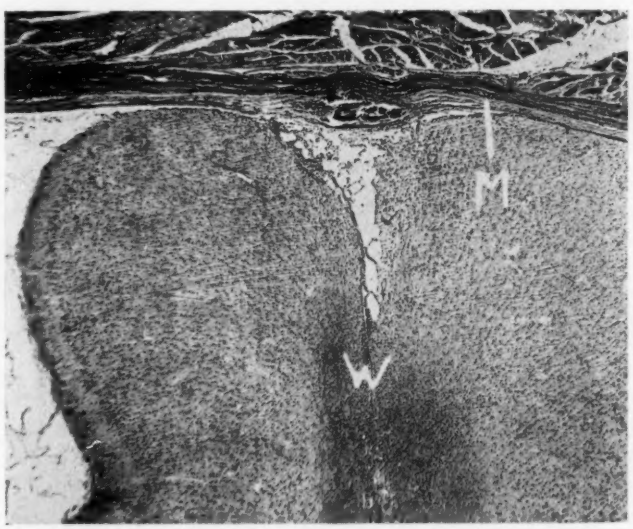

Fig. 5.—Attenuated amniotic membrane (*M*) thirty days following implantation; encapsulation and cellular reaction are minimal. The inner layer of the capsule is adherent to the cerebral wound (*W*). Hematoxylin and van Gieson stains.

Methods and Materials.—This membrane is prepared from the allantois of the gravid bovine uterus.* Cattle and other ungulate (hoofed) mammals are an excellent source of this material. In these animals the allantois reaches a large size and serves as an embryonic organ of respiration, nutrition, and excretion. It is composed of a

*Insultoic membrane was supplied by the Lewis Mfg. Co., Bauer & Black, divisions of the Kendall Company, Chicago, Ill.

mesenchymal layer, containing a large number of blood vessels, and has an entodermal lining.

For surgical use the membrane is prepared as follows. After a careful dissection of the membrane from the uterus it is cleaned by repeated washing in water. The membrane is then chromicized, stretched on gauze-covered boards, and dried. Pieces of the desired size are cut, placed in open tubes, and dehydrated in ovens. The method of sterilization is that employed for catgut, namely, immersion in light hydrocarbon oil for one hour at 155° C. Following this stage the oil is drained off and the tubes filled with 100 per cent ethanol containing 0.1 per cent of potassium mercuric iodide. Finally, the glass tubes are sealed and the membrane is ready for use.

Both the single and the double thickness chromicized membranes were used in the present series of experiments. They were thoroughly washed in physiologic saline solution prior to emplacement on the brain.

Experimental Results.—This membrane was used in five animals for periods of time varying from twenty-four to eighty-five days. In all of the experiments the membrane was treated as a foreign body and walled off by dense connective tissue (Fig. 6). The inner layer of the capsule

Fig. 6.—After sixty-three days single thickness allantoic membrane (*M*) is invested in dense connective tissue. The inner face of this capsule is bound to both the cerebral wound (*W*) and pia-arachnoid over the crown of the wounded gyrus. Hematoxylin and van Gieson stains.

was invariably adherent to the cerebral wound. A further evidence of tissue irritation was the presence of foreign body giant cells, small round cells, and phagocytes, at times in large numbers. The phagocytes were especially numerous during the period when resorption of the membrane was most active. Although both the single and double

thickness membranes were still recognizable in the sections at the end of eighty and eighty-five days, respectively, there was sufficient resorption at the end of sixty days to allow fibroblasts to proliferate through the clefts between the fragments. The experience with amnioplastin allows the assumption that when resorption of the membrane has been completed the cavity of the capsule would be entirely obliterated due to the fusion of its inner and outer walls. By this process the former plane of separation becomes the site of a firm attachment.

Cargile Membrane

Historical Survey.—In 1902, Morris[45] reported the use of prepared ox peritoneum for the prevention of postoperative peritoneal adhesions in human cases. He named this membrane in honor of Dr. Charles H. Cargile of Bentonville, Ark., who suggested its use. Morris reported good clinical results but subsequent observations on the condition of the membrane were not made.

Although Morris was a pioneer in the use of membranes of peritoneal derivation, he was preceded by Baum.[2] In 1894, Baum reported satisfactory clinical results following the use of the prepared peritoneum of freshly slaughtered calves to protect traumatized peritoneal surfaces. Later exposures of the membrane and protected surfaces were not mentioned.

In his original article Morris mentioned the close adherence of Cargile membrane to exposed brain tissue and intimated that it may be of value as temporary dura mater. He does not describe experiments to confirm this impression. Craig and Ellis[13] were the first to attempt dural repair with Cargile membrane. They reported experiments in which this material was employed for dural restoration in dogs. Unfortunately, all of their results were vitiated due to suppuration in the wounds.

Prime[55] pioneered in the use of Cargile membrane for the specific purpose of preventing adhesions between the brain and its coverings. However, in his experiments the membrane was encapsulated and adhesions were invariable if the cortex was traumatized.

These early observations on Cargile membrane were followed by reports on other viable and nonviable membranes of peritoneal derivation. In practically all instances the purpose of the membrane was the closure of dural defects. Included in this group are membranes derived from hernia sacs, omentum, and the parietal and visceral peritoneal reflections. Satisfactory results have been obtained when these peritoneal membranes were used only as dural substitutes. Meningocerebral adhesions occurred invariably if the brain had been damaged.

Cargile membrane has been frequently recommended in the surgery of peripheral nerve injuries. In 1919, Joyce[33] described the use of the prepared membrane of a fine variety to protect nerves following either suture or neurolysis. Four of his cases were re-explored three, four,

seven, and nineteen months later. From his observations on these cases he concluded that the membrane is absorbed in less than six months. During this time it fulfils its purpose as a protective against adhesion formation.

Huber[30] also reported satisfactory results following the use of Cargile membrane. The commercial type of membrane was absorbed in ten days and felt to be unsatisfactory. However, if this material was placed in 70 per cent, followed by absolute, alcohol and then dried, his results were better. The alcoholized membrane was not absorbed within five to six months and during this time protected the nerve and incited only a minimal connective tissue reaction. His results with formolized arterial sheaths, fat, and fascia lata were much less satisfactory. Cairns and Young[10] considered the fresh membrane as being superior to the alcoholized form. They remark that the latter type causes a greater tissue reaction around the nerve.

In addition to his experimental studies of amniotic and allantoic membranes, Johnson[31] employed Cargile membrane to prevent peritoneal adhesions. In all of his experiments the membrane was treated as a foreign body and the results were uniformly poor.

Chao and his co-workers[12] used Cargile membrane in their studies of the prevention of meningocerebral adhesions in cats. They found dense adhesions and a moderate cellular response in all of the experiments.

In summary, therefore, the experience with Cargile membrane over the wounded brain and peritoneum has been generally unsatisfactory. Nevertheless, due to the availability of large amounts of this material, the promise it has shown in peripheral nerve surgery and the lack of adequate study of its usefulness in the prevention of meningocerebral adhesions, we have subjected it to further investigation.

Methods and Materials.—The commercial, unchromicized Cargile membrane* was employed. This membrane is derived from the submucous layer of the ox cecum. It is prepared according to the method used for catgut, namely, washing, drying, and sterilization by heating in a light hydrocarbon oil. The result of this process is a thin, translucent, and pliable membrane that conforms nicely to the convolutional pattern of the brain over which it is placed.

Experimental Results.—Cargile membrane was used in five cats. The animals were killed at intervals extending from four to ninety days. These membranes have failed to prevent meningocerebral adhesions in all of the experiments. The type of reaction is essentially similar to that noted with insultoic membrane. Again there is formation of a dense connective tissue capsule (Fig. 7) and a variable inflammatory cell pattern involving foreign body giant cells, small round cells, and phagocytes. At the end of sixty days the membrane had undergone only slight resorption. However, at the end of ninety days it was fragmented and the cavity of the capsule bridged by the proliferation

*Kindness of Johnson & Johnson, New Brunswick, N. J.

of connective tissue between these fragments. Finally, the inner surface of the capsule was tenaciously adherent to the cerebral wound in all of the experiments.

Tantalum

Historical Survey.—In 1940, Burke[9] introduced tantalum, a new metal for surgical use. In contrast to the stainless steels and vitallium, both of which are alloys, tantalum is an element. Pure tantalum is bluish gray, soft, malleable and ductile. It is resistant to most organic reagents except those which contain fluorine, free sulfur trioxide, or strong alkalis.

Burke used tantalum in the form of bone plates and screws in dogs and rabbits, and as a skin suture in thirty-four human cases. In all of these instances there was a lack of tissue irritation. The observations of Burch and Carney[7] on tantalum bone plates and screws and sutures are confirmatory. Recently, one of us (R. H. P.) has shown that strips of tantalum ribbon may be embedded in cerebral tissue without provoking an inflammatory reaction. In view of these findings it was believed that thin sheets of this metal would be of value in the prevention of meningocerebral adhesions.

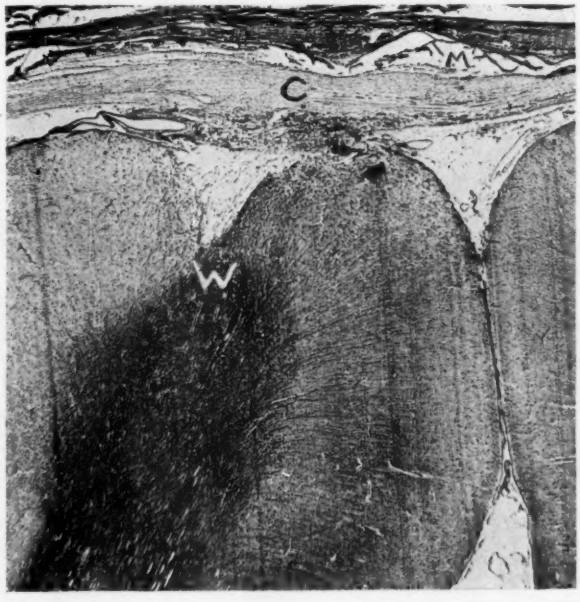

Fig. 7.—Cargile membrane (*M*) after sixty days; the thick inner layer of the capsule (*C*) is intimately bound to the cerebral wound (*W*) by the connective tissue core. Hematoxylin and van Gieson stains.

Methods and Materials.—Tantalum foil* of 0.001 of an inch thickness was used. A thinner foil is preferable but impossible to obtain. Due to the physical characteristics of the grain structure of this metal, fully annealed, homogeneous sheets less than 0.001 of an inch in thickness cannot be rolled.

*Courtesy of the Fansteel Metallurgical Corporation, North Chicago, Ill.

The pieces of foil, cut to the desired size, were sterilized either by boiling or autoclaving. Before the sheets were applied to the brain surface they were bent to conform to the cortical contour and all sharp corners were rounded off.

Experimental Results.—The reactions to tantalum foil have been observed in six animals over a period ranging from 10 to 143 days. In all of the experiments there has been only a minimal reaction of connective tissue and other cellular elements. Encapsulation has been comparatively slight. The attachment between the cerebral wound and overlying dura has been an indirect one by way of the margin of this capsule (Fig. 8). Giant cells were found in one of the experiments but were few in number. There was no reaction involving small round

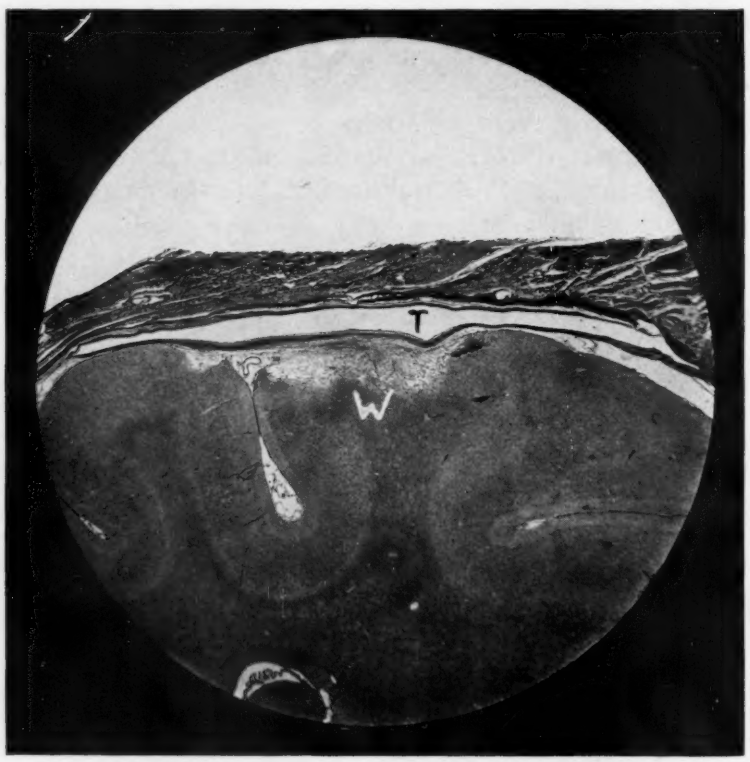

Fig. 8.—Result thirty days following implantation of tantalum foil; the inner layer of the capsule previously occupied by the tantalum (*T*) is adherent to the cerebral wound (*W*). Hematoxylin and van Gieson stains.

cells, polymorphonuclear leucocytes, or phagocytic cells. In one animal killed at the end of seventy-nine days, the capsule formation was exceptionally slight and the cerebral wound was bridged by a membrane histologically identical with the arachnoid. The removed pieces of tantalum had their original luster. There was no evidence that any corrosion had occurred.

Polyvinyl Alcohol

Historical Survey.—The search for materials in which the rate of resorption in the tissues could be controlled disclosed the polymerized

vinyl alcohol compounds. These substances are used commercially in the manufacture of shatterproof glass. Their chief attraction in the present study is the change in the solubility rate obtainable by modifying their structural formulas. The replacement of the hydroxyl groups of polyvinyl alcohol with acetate groups eventually changes the compound to polyvinyl acetate. The compounds formed in the stages of transition vary in their solubility. Maximum solubility is obtained when approximately 20 per cent of the hydroxyl groups have been replaced by acetate groups. Pure polyvinyl alcohol and polyvinyl acetate are less soluble than this 20 per cent compound. One, therefore, has the choice of these substances in a wide range of solubility.

In 1938, Dötzer[18] reported experiments on the reactions of bacteria in contact with polyvinyl alcohol. Colon bacilli, streptococci, staphylococci, pneumococci and tubercle bacilli were inoculated in nutrient media containing either pure polyvinyl alcohol or polyvinyl alcohol, with hydroxyquinoline potassium sulfate added in concentrations of 0.1 per cent and 0.16 per cent. Pure polyvinyl alcohol was found to be bacteriostatic but not bactericidal. However, with the addition of the small amounts of antiseptic, most of the bacteria were killed when the ratio of polyvinyl alcohol to culture media was 1:1 and all were killed when this ratio was 10:1. In his report Dötzer mentions the animal experiments of Braun and Herrmann in which polyvinyl alcohols were used. Unfortunately the results of these experiments are not described.

Methods and Materials.—In the problem under consideration the most favored compound would be the one which would remain intact for at least one month. This length of time would permit the pia-arachnoid to carpet a small cerebral wound without the interference of invading connective tissue cells derived from the dura and other overlying structures. On the basis of solubility in human cerebrospinal fluid in vitro at 37° C., a polymerized vinyl alcohol* having a 5 per cent replacement of hydroxyl groups with acetate groups and a viscosity of 15 centipoises was selected.

The material was made into extremely thin, transparent films resembling a fine grade of cellophane. These films were inserted between sheets of filter paper, placed over a water bath, and sterilized in an electric oven at 100° C. for forty-five minutes. The absence of bacteria in the films was confirmed by aerobic and anaerobic culture. Prior to their use on the cerebral cortex, the sheets were moistened in physiologic saline solution.

Experimental Results.—The 5 per cent polyvinyl alcohol films were used in five animals. The period of observation varied from ten to sixty-six days. In all of the experiments the results were disappointing. Invariably, the membrane was invested in a thick connective capsule, the inner surface of which was firmly adherent to the cerebral

*Courtesy of Shawinigan Chemicals Ltd., Shawinigan Falls, P. Q.

wound. Giant cells were particularly prominent in the inflammatory reaction (Fig. 9). Aggregations of phagocytes and small round cells were scattered throughout the capsule. In addition, pools of homogeneous material, which stained a bright pink with acid fuchsin, were found in the capsular interstices. At the end of 66 days the membrane was for the most part intact but showed a moderate amount of swelling suggesting beginning resorption.

DISCUSSION

While this study has failed to disclose an ideal material for the prevention of meningocerebral adhesions, it is not without value. In addition to confirming or denying the results of past workers, it has disclosed certain factors which must be considered in the ultimate solution of the problem.

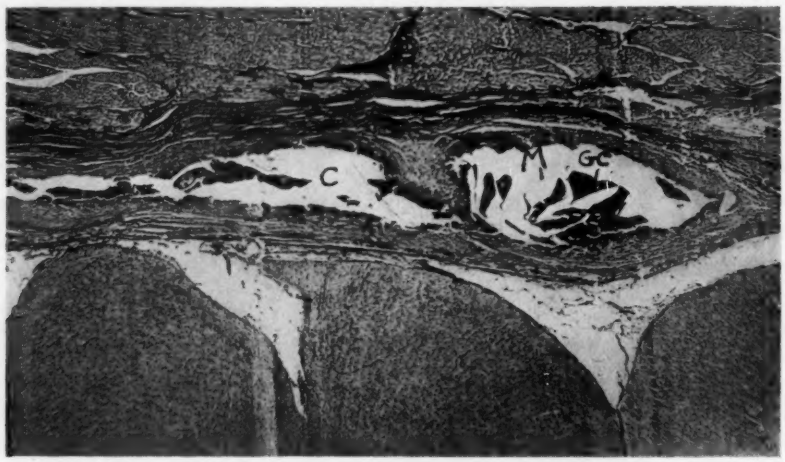

Fig. 9.—Dense encapsulation (*C*) and cellular reaction surrounding the polyvinyl alcohol membrane (*M*); the capsule is adherent to the cerebral wound (*W*). Giant cells (*GC*) are prominent. Period of observation, sixty-six days; hematoxylin and van Gieson stains.

All of the materials, without exception, have been encapsulated. This capsule is derived principally from the dura and to a lesser extent from the arachnoid. Its pattern, thickness, and cellularity have varied with the material used. As long as the membrane remains intact the inner and outer layers of the capsule are separable. However, with the onset of resorption, fibroblasts grow through the defects in the membrane, fuse the inner and outer connective tissue walls, and eventually obliterate the capsular space. In addition to the fibroblastic activity, there has been an inflammatory reaction which has varied with each material. The character of the individual reactions may now be considered.

Tantalum foil was superior to all of the materials employed. Encapsulation of the metal was comparatively slight even at the end of 143 days. In an animal killed after seventy-nine days the inner layer of the capsule consisted of slightly thickened arachnoid which had al-

ready bridged the cerebral wound. Other than a few foreign body giant cells noted in the capsular space in one experiment, there was no inflammatory reaction. Furthermore, the removed pieces of foil had their original luster, suggesting a complete absence of corrosion in the tissues.

The resorbable membranes, namely amnioplastin, allantoic membrane, and Cargile membrane, may be considered as a group since the response of the tissues to all of them is essentially similar. The thickness of the capsule investing these membranes is modified by two factors, namely, the extent of wrinkling, and the resorption time of the membrane. The folds of the wrinkled membrane are invaded by fibroblasts with a resulting greater thickness of the capsule in these areas. In general, the capsule formation was a continued proliferation of connective tissue which did not cease until the membrane disappeared. Amnioplastin was absorbed more quickly than the other materials, usually requiring thirty to forty days. If left in alcohol for several days before use, or boiled instead of autoclaved, it required a longer period of time. The epithelial layer disappeared more quickly than the connective tissue stratum. Chromicized single and double thickness allantoic membranes were histologically demonstrable in the tissues at the end of eighty and eighty-six days, respectively, but were fragmented and undergoing active resorption. Cargile membrane was for the most part intact at the end of ninety days, although phagocytosis had commenced and fragmentation was rather extensive.

As noted previously, the onset of fragmentation and resorption of these membranes was followed by proliferation of the cells lining the capsular space with eventual fusion of the inner and outer walls. The absorbable membranes have, therefore, not only failed to prevent meningocerebral adhesions but have provoked a reaction probably greater than would have occurred had they not been used. Lastly, all of these materials have stimulated an inflammatory reaction with a variable pattern involving foreign body giant cells, small round cells, and phagocytes. In the experiments with amnioplastin the inflammatory reaction was greater on the epithelial side of the membrane.

It is obvious from the large number of experiments on amnioplastin that the chief purpose of this study was to determine whether or not the continued clinical use of this material was justified. We now believe that the use of this material for the prevention of meningocerebral adhesions is not warranted. It is difficult to account for the discrepancies between the results obtained by Chao, Humphreys, and Penfield[12] and the findings in the present study. In our earlier experiments the technique for preparation of the amnion, as outlined by these authors, was rigidly followed. The finding of meningocerebral adhesions in all of the experiments with the membrane so prepared led to the many other methods of fixation, fat extraction, sterilization, and preservation. Furthermore, the emplacement of the membrane over the

cerebral wound was controlled so that we knew if the epithelial or connective tissue layer was in contact with the brain.

There was but one good result in the ninety-four experiments with amnioplastin. This animal was killed at the end of 118 days. The membrane had been prepared by fixation in a series of alcohols, extraction of the fat in ether, drying, and autoclaving. Membranes prepared in exactly the same way produced adhesions in other animals.

When last heard from in April, 1940, Chao, in Peiping, was still enthusiastic about amnioplastin. He had used the material in a series of operations on human cases and believed that it was satisfactory. Unfortunately, due to the war, no further correspondence has been received and we are unaware of his present impression of this material.

Both the fresh and attenuated forms of amniotic membrane have failed to prevent meningocerebral adhesions. Nevertheless, certain observations on these materials are worthy of mention. The most interesting feature is the histologic evidence for the viability of their connective tissue layers. The collagen fibers were sharply demarcated with the characteristic large, oval, vesicular nuclei of fibroblasts scattered among them. There was no evidence that these nuclei belonged to fibroblasts which had infiltrated from the adjacent tissues.

The chief difference between the fresh and attenuated amnion lies in the reaction of the surrounding tissues to their presence. Large aggregations of polymorphonuclear leucocytes or small round cells were constantly present along both surfaces of the fresh membrane, particularly on the epithelial side. The response of the encapsulating connective tissue cells was similarly intense. In contrast, the attenuated membrane provoked but minimal capsule formation and inflammatory reaction. Other than a few aggregations of small round cells in one experiment, inflammatory cells were lacking. The method of attenuation had apparently inactivated the irritating factor in the fresh membrane.

In all of the experiments the implantation of the polyvinyl alcohol films was followed by encapsulation in dense connective tissue and an intense inflammatory reaction involving cells of many types. The reaction has been more severe than with any of the other materials. The films were still intact at the end of sixty-six days, a much longer time than was anticipated. It is possible that a more soluble compound would have been less irritating.

From the practical standpoint, therefore, none of the materials can be recommended for permanent use over the wounded brain. Tantalum foil and the resorbable animal membranes may be practical for the temporary separation of layers, for example, between stages of a two-stage craniotomy. If used for this purpose it would be necessary to carry out the second stage before appreciable resorption had occurred.

Since our study has been limited to the use of these materials for the prevention of meningocerebral adhesions alone, we are not qualified to

sanction or condemn their use in other surgical procedures. Satisfactory results with many of these substances have been reported by other observers. Furthermore, a detailed study of any one material, other than amnioplastin, has not been carried out. Nevertheless, we wish to re-emphasize that in our studies all of these materials, both resorbable and nonresorbable, were treated as foreign bodies and encapsulated in connective tissue. Furthermore, resorption of the membranes was followed by a fusion of the inner and outer layers of this capsule. Due to these factors, the membranes not only failed to prevent meningocerebral adhesions but probably contributed to their formation.

SUMMARY AND CONCLUSIONS

The experiments in this study concern the development of a material for use in the prevention of adhesions between the wounded brain and its coverings. The investigation was stimulated by the high incidence of epilepsy following open craniocerebral injuries, particularly those due to missiles. In the introduction we have discussed the theoretical significance of the meningeal ingrowth of cerebral scar in the causation of post-traumatic epilepsy. The literature bearing on the problem is reviewed.

Seven different materials, namely, human amniotic membrane in fresh, attenuated and fixed (amnioplastin) forms, beef allantoic (Insultoic) membrane, Cargile membrane, sheets of the metal tantalum .001 inch in thickness, and films of 5 per cent polyvinyl alcohol were used. These substances were placed over both the wounded and unwounded cerebral hemispheres of a large number of cats. The animals were killed at appropriate intervals varying from 4 to 240 days. Gross and microscopic observations of the tissue reactions to the materials are reported. The following conclusions are drawn:

1. All of these materials are foreign bodies and are eventually encapsulated. The connective tissue and inflammatory cell reaction are variable in intensity. Although a few of them show promise, none can be considered as having offered a solution to the problem.

2. Tantalum foil was surprisingly inert and provoked but minimal encapsulation and inflammatory reaction. Being an impermeable material the meningocerebral attachment was an indirect one via the margin of the capsule.

3. With the resorbable membranes, namely, amnioplastin, insultoic membrane, and Cargile membrane, the connective tissue investment and inflammatory cell response were more pronounced. Resorption of these materials was followed by fusion of the inner and outer layers of the capsule with resultant binding of the brain and dura through the medium of dense connective tissue.

4. The fresh and attenuated amniotic membranes did not prevent meningocerebral adhesions but are of interest because of the histologic evidence for survival of their connective tissue layers.

5. The 5 per cent polyvinyl alcohol films caused an intense inflammatory and fibroblastic reaction. However, this may be due to the fact that the compound used in this study was too insoluble.

6. Tantalum foil and the resorbable membranes (amnioplastin, allantoic, and Cargile membrane) may be of value for the temporary separation of layers, e.g., in a two-stage craniotomy. Use of these materials for permanent emplacement over the wounded brain is not recommended.

The authors wish to express their gratitude to Dr. Wilder Penfield, whose encouragement and guidance throughout this study have been invaluable.

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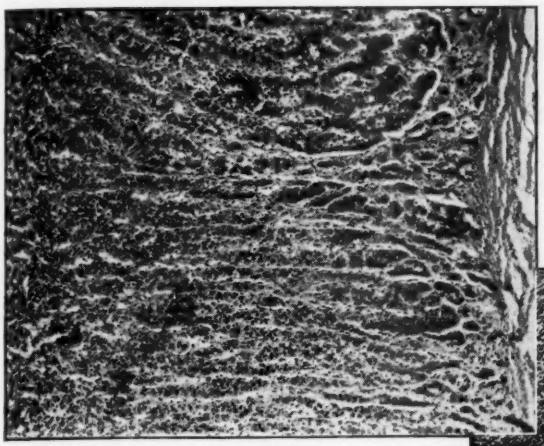
ADRENAL CORTICAL STEROIDS ESSENTIAL TO LIFE



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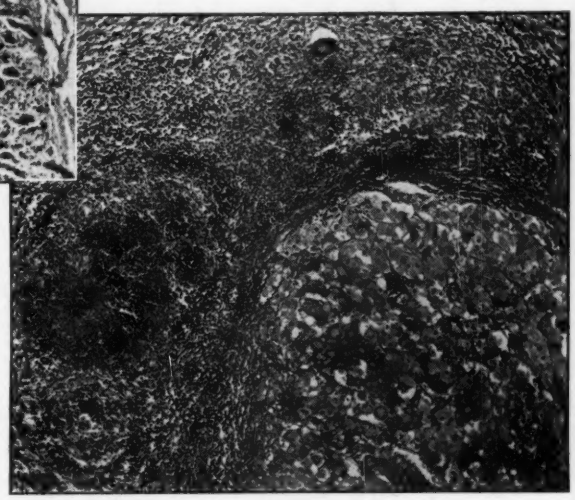

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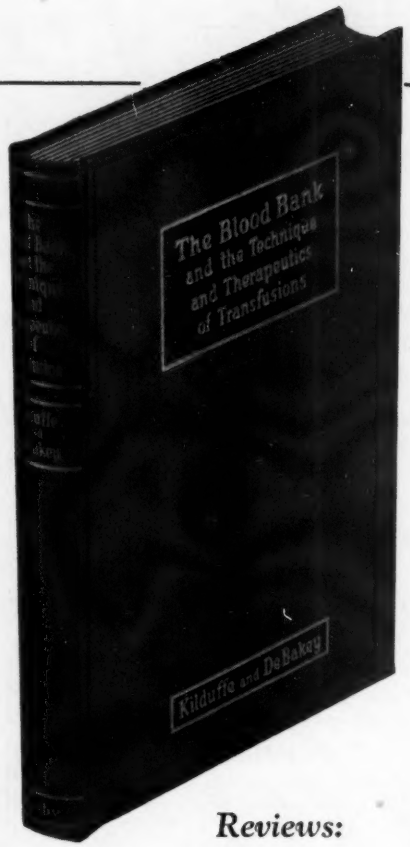

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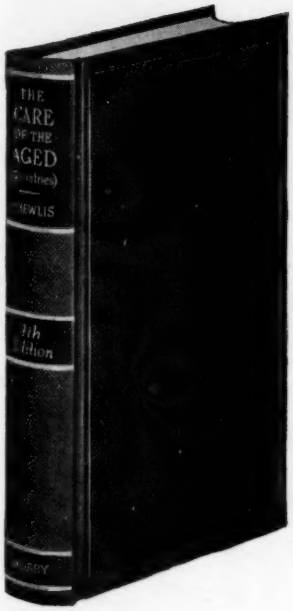

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